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# BRONCHOCONSTRICTION INDUCED BY SEROTONIN, DIAZOXIDE, AND ORTHODROMIC STIMULATION OF THE GLOSSOPHARYNGEAL NERVE

BY

© Margaret A. Peterson

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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(PHARMACOLOGY)

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Date...22 APRIL 1981......

DEDICATED TO

MY FAMILY AND FRIENDS

προαιρεῖσθαι τε δεῖ ἀδύνατα εἰκότα μᾶλλον ἢ δυνατὰ ἀττίθανα...

...Plausible impossibilities should be preferred to unconvincing probabilities,

Aristotle, Poetics, xxiv.

# ABSTRACT

The effects of serotonin (5HT) and diazoxide on the airways of anesthetized, paralyzed guinea-pigs were examined.

The injection of 5HT produced constriction in the large airways of these animals in two ways. Firstly, constriction was produced by a direct action of 5HT, on airway smooth muscle, which was blocked by the 5HT-antagonist, methysergide.

Secondly, 5HT was shown to have an indirect action which involved a central autonomic reflex that was independent of the vagus nerves. The afferent pathway of this reflex involved fibres in the glossopharyngeal nerves. The efferent pathway was not completely characterized but appeared to have both peripheral muscarinic and sympathetic components; the sympathetic component most likely involved alpha$_2$-receptors.

The effects of 5HT on the small airways of these animals were not reproducible. Therefore, no mechanism(s) could be determined for these actions.

Diazoxide also produced constriction of the large airways by an indirect action. This action was also shown to involve a non-vagal, central autonomic reflex, mediated by afferent fibres in the glossopharyngeal nerves. This reflex did not have a muscarinic component, but did involve a sympathetic component similar to the one associated with responses to 5HT. In addition, the reflex effects of diazoxide were blocked by mepyramine, indicating the involvement of histamine $H_1$-receptors. These responses were also blocked by disodium cromoglycate (DSCG), suggesting that $H_1$-receptor stimulation was due to the release of histamine.

Electrical stimulation of the carotid sinus nerve produced reflex bronchoconstriction which was dependent on the pulse-width, and which consisted of two components.

One component was blocked by atropine or atropine methiodide, whereas the other was blocked by either mepyramine or DSCG. Both components were unaffected by vagotomy, but were abolished by trimethaphan, catecholamine depleting agents, or decentralization. Thus, nerve stimulation produced reflex constriction similar to that produced by 5HT and diazoxide, and confirmed that the afferent pathways of their reflex actions were mediated by the glossopharyngeal nerves.

Several observations made in these investigations are of possible clinical interest. Firstly, reflex bronchoconstriction induced by 5HT or diazoxide was selectively blocked by muscarinic or histaminergic antagonists, respectively. These results suggest that appropriate drug therapy should be as effective as unilateral or bilateral removal of the carotid body with, or without, carotid sinus denervation in the treatment of intractable asthma.

Secondly, this work suggested that an investigation of alpha$_2$-agonists and antagonists might be helpful in resolving the controversy as to whether or not alpha-receptors exist in the airways.

Lastly, the block of bronchoconstriction induced by diazoxide or nerve stimulation revealed a previously unreported action of DSCG. The ability of DSCG to prevent reflex constriction may partially explain its ability to reduce airway hyperreactivity associated with lung disease or induced by various other agents such as acetylsalicylic acid.

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# TABLE OF CONTENTS

PAGE

INTRODUCTION........................................................ 1

METHODS AND MATERIALS.................................................. 24

Animal Preparation.................................................. 25

Determination of $R_L$.................................................. 27

Determination of $C_L$.................................................. 28

Measurement of Blood Pressure.................................................. 28

Nerve Section.................................................. 29

Carotid Nerve Stimulation.................................................. 29

Decentralization.................................................. 30

Statistical Analysis.................................................. 30

RESULTS.................................................. 31

A. Experiments Involving 5HT.................................................. 33

Effects of 5HT on $R_L$ and $C_L$.................................................. 33

Effects of methysergide.................................................. 34

Effects of muscarinic blockade.................................................. 34

Effects of combinations of methysergide and muscarinic blockers.................................................. 34

Effects of ganglionic blockade.................................................. 35

Effects of vagotomy.................................................. 36

Effects of glossopharyngealotomy.................................................. 37

Effects of decentralization.................................................. 38

Effects of mepyramine and disodium cromoglycate.................................................. 38

Effects of catecholamine depleting agents.................................................. 39

Effects of propranolol.................................................. 40

Effects of azapetine.......................................... 41

Effects of clonidine.......................................... 41

B. Experiments Involving Diazoxide............................ 43

Effects of trimethaphan....................................... 43

Effects of glossopharyngealotomy.............................. 44

Effects of decentralization................................... 44

Effects of disodium cromoglycate.............................. 44

Effects of catecholamine depleting agents..................... 45

Effects of propranolol........................................ 45

Effects of azapetine.......................................... 45

Effects of clonidine.......................................... 46

C. Experiments Involving Stimulation Of The Carotid Sinus Nerve 47

Effects of carotid sinus nerve stimulation in normal and vagotomized animals.......................................... 47

Effects of trimethaphan....................................... 48

Effects of decentralization................................... 48

Effects of muscarinic blockade................................ 48

Effects of mepyramine and disodium cromoglycate............... 48

Effects of catecholamine depletors............................ 49

Effects of clonidine.......................................... 50

DISCUSSION.................................................... 51

TABLES........................................................ 67

FIGURES....................................................... 71

REFERENCES.................................................... 132

APPENDIX 1.................................................... 149

APPENDIX 2.................................................... 150

CURRICULUM VITAE.............................................. 154

## LIST OF TABLES

| TABLE | DESCRIPTION | PAGE |
|---|---|---|
| 1. | Results of Stimulation Experiments | 67 |
| 2. | Effects of Various Drugs and Treatments on $R_L$ and $C_L$ | 68 |
| 3. | Baseline Values of $R_L$ and $C_L$ | 70 |

# LIST OF FIGURES

| FIGURE | DESCRIPTION | PAGE |
|---|---|---|
| 1. | The major subdivisions of the airways | 71 |
| 2. | Some structural components of the airways | 72 |
| 3. | The large and small airways | 73 |
| 4. | Nervous pathways associated with reflex bronchoconstriction | 74 |
| 5. | The general location of the carotid sinus and carotid body | 75 |
| 6. | Apparatus for measurements of $R_L$ and $C_L$ | 76 |
| 7. | Effects of 5HT on $R_L$ | 77 |
| 8. | Effects of 5HT on $C_L$ | 78 |
| 9. | Effects of methysergide (M), followed by atropine (ATR), on 5HT-induced increases in $R_L$ | 79 |
| 10. | Effects of atropine (ATR), followed by methysergide (M), on 5HT-induced increases in $R_L$ | 80 |
| 11. | Effects of atropine methiodide (AMI) on 5HT-induced increases in $R_L$ | 81 |
| 12. | Effects of atropine methiodide (AMI), followed by atropine (ATR), on 5HT-induced increases in $R_L$ | 82 |

13. Effects of atropine methiodide (AMI), followed by methysergide (M), on 5HT-induced increases in $R_L$ 83

14. Effects of trimethaphan (TRI), followed by methysergide (M), on 5HT-induced increases in $R_L$ 84

15. Effects of trimethaphan (TRI), followed by atropine (ATR) and then methysergide (M), on 5HT-induced increases in $R_L$ 85

16. Effects of bilateral, mid-cervical vagotomy, followed by atropine (ATR), on 5HT-induced increases in $R_L$ 86

17. Effects of bilateral, high vagotomy, followed by atropine (ATR), on 5HT-induced increases in $R_L$ 87

18. Effects of bilateral glossopharyngealotomy, followed by atropine (ATR) and then methysergide (M), on 5HT-induced increases in $R_L$ 88

19. Effects of bilateral glossopharyngealotomy, followed by methysergide (M), on 5HT-induced increases in $R_L$ 89

20. Effects of methysergide (M) on 5HT-induced increases in $R_L$ obtained in animals after either left (L) or right (R) unilateral glossopharyngealotomy (UG) had been performed 90

21. Effects of mepyramine (MEP) on 5HT-induced increases in $R_L$ 91

22. Effects of disodium cromoglycate on 5HT-induced increases in $R_L$ 92

23. Effects of atropine (ATR), followed by methysergide (M), on 5HT-induced increases in $R_L$ observed in animals pretreated with reserpine (RES) 93

24. Effects of methysergide (M) on 5HT-induced increases in $R_L$ obtained in animals pretreated with reserpine (RES) 94

25. Effects of atropine (ATR), followed by methysergide (M), on 5HT-induced increases in $R_L$ obtained in animals pretreated with 6-hydroxydopamine (6HD), 35 mg/kg 95

26. Effects of methysergide (M) on 5HT-induced increases in $R_L$ obtained in animals pretreated with 6-hydroxydopamine (6HD), 35 mg/kg 96

27. Effects of bretylium (BRE), followed by atropine (ATR), methysergide (M) and then dexamphetamine (DEX), on 5HT-induced increases in $R_L$ 97

28. Effects of bretylium (BRE), followed by methysergide (M) and then dexamphetamine (DEX), on 5HT-induced increases in $R_L$ 98

29. Effects of propranolol (PRO) on 5HT-induced increases in $R_L$ 99

30. Effects of azapetine (AZP, 0.5 mg/kg) on histamine (HIS)-induced increases in $R_L$ and effects of AZP (0.5 mg/kg), followed by methysergide (M), on 5HT-induced increases in $R_L$ 100

31. Effects of azapetine (AZP), 1 mg/kg, on 5HT-induced increases in $R_L$ 101

32. Effects of azapetine (AZP), 1 mg/kg, on histamine (HIS)-induced increases in $R_L$ 102

33. Effects of clonidine (CLD), followed by methysergide (M), on 5HT-induced increases in $R_L$ 103

34. Effects of diazoxide on $C_L$ 104

35. Effects of diazoxide on $R_L$ 105

36. Effects of trimethaphan (TRI) on responses to diazoxide, 40 mg/kg 106

37. Effects of bilateral (B) and left (L) or right (R) unilateral glossopharyngealotomy on increases in $R_L$ produced by diazoxide, 40 mg/kg. 107

38. Effects of decentralization on responses to diazoxide, 20 mg/kg 108

39. Effects of disodium cromoglycate (DSCG) on control responses to diazoxide, 40 mg/kg 109

40. Effects of disodium cromoglycate, 10 mg/kg, on histamine-induced increases in $R_L$ 110

41. Effects of bretylium (BRE), and BRE followed by dexamphetamine (DEX), on control responses (C) to diazoxide, 40 mg/kg 111

42. Effects of azapetine (AZP) and clonidine (CLD) on control responses (C) to diazoxide, 40 mg/kg 112

43. Changes in $R_L$ produced by nerve stimulation at 2 or 4 V 113

44. Changes in $C_L$ produced by nerve stimulation at 2 or 4 V 114

45. Effects of bilateral, mid-cervical vagotomy on increases in $R_L$ produced by nerve stimulation 115

46. Mean responses to nerve stimulation obtained at intervals over periods of two to three hours 116

47. Effects of atropine (ATR, 0.05 & 0.1 mg/kg) on increases in $R_L$ produced by nerve stimulation 117

48. Effects of atropine methiodide (AMI, 0.05 & 0.1 mg/kg) on increases in $R_L$ produced by nerve stimulation 118

49. Effects of atropine methiodide (AMI, 0.05 mg/kg), followed by atropine (ATR), on increases in $R_L$ produced by nerve stimulation 119

50. Effects of mepyramine (MEP, 0.1 & 0.2 mg/kg) on increases in $R_L$ produced by nerve stimulation 120

51. Effects of disodium cromoglycate (DSCG) on increases in $R_L$ produced by nerve stimulation 121

52. Effect of disodium cromoglycate (DSCG), followed by mepyramine (MEP, 0.1 mg/kg), on increases in $R_L$ produced by nerve stimulation 122

53. Effects of mepyramine (MEP, 0.1 & 0.2 mg/kg), followed by atropine (ATR, 0.05 mg/kg) on increases in $R_L$ produced by nerve stimulation 123

54. Effects of atropine methiodide (AMI, 0.05 & 0.1 mg/kg), followed by mepyramine (MEP, 0.1 mg/kg), on increases in $R_L$ produced by nerve stimulation 124

55. Effects of atropine methiodide (AMI, 0.1 mg/kg), followed by disodium cromoglycate (DSCG, 10 mg/kg) on increases in $R_L$ produced by nerve stimulation 125

56. Effects of atropine (ATR, 0.1 mg/kg), followed by disodium cromoglycate (DSCG, 10 mg/kg) on increases in $R_L$ produced by nerve stimulation 126

57. Effects of 6-hydroxydopamine (6HD) on increases in $R_L$ produced by nerve stimulation 127

58. Effects of bretylium (BRE), and BRE followed by dexamphetamine (DEX), on increases in $R_L$ produced by nerve stimulation 128

59. Effects of bethanidine (BET), and BET followed by dexamphetamine (DEX), on increases in $R_L$ produced by nerve stimulation 129

60. Possible reflex arcs associated with reflex actions of 5HT 130

61. Possible reflex arcs associated with reflex actions of diazoxide 131

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AMI | Atropine methiodide |
| ATR | Atropine |
| AZP | Azapetine |
| BET | Bethanidine |
| BRE | Bretylium |
| $C_6$ | Hexamethonium |
| $C_L$ | Pulmonary compliance |
| CLD | Clonidine |
| DEX | Dexamphetamine |
| DSCG | Disodium cromoglycate |
| 5HT | Serotonin; 5-hydroxytryptamine |
| 6HD | 6-Hydroxydopamine |
| M | Methysergide |
| MEP | Mepyramine |
| NS | Nerve stimulation |
| $P_R$ | Resistive force in airways |
| $P_T$ | Transpleural pressure (estimated as tracheal pressure) |
| PHE | Phenylephrine |
| PRO | Propranolol |
| RES | Reserpine |
| $R_L$ | Pulmonary flow resistance |
| TRI | Trimethaphan |
| V | Respiratory volume |
| $\dot{V}$ | Rate of airflow |

# CHAPTER 1

# INTRODUCTION

The major functions of the respiratory system are to provide oxygen to the body and to remove carbon dioxide from the body. Optimal functioning requires that two separate, but related, processes occur efficiently (Guyton, 1971a). Firstly, adequate movement of air into and out of the lungs must occur, and secondly, oxygen and carbon dioxide must diffuse across alveolar membranes. Both processes depend, to varying degrees, on the patency of the airways. Therefore, some anatomy and physiology of the lungs will be reviewed in order to explain the more common mechanisms involved in airway obstruction or narrowing.

The trachea is the largest of the airways and divides to form the bronchi (see Figure 1). The bronchi repeatedly subdivide, causing the airways to become progressively shorter and of smaller diameter with each division. The smallest of the bronchi are referred to as bronchioles. Terminal bronchioles lie between those airways which conduct air and those airways which are involved in gas exchange (West, 1974). The terminal bronchioles lead into the respiratory bronchioles which may open directly into an alveolus but which more often branch into several alveolar ducts. The alveolar ducts are short airways connecting respiratory bronchioles to alveoli; the alveoli are the major sites of gas exchange.

The actions of cilia, goblet cells, and bronchial glands are all important to the maintenance of patent airways (see Figure 2). Cilia are found in the airway mucosa to the level of the terminal bronchioles (West, 1974a; Kleinerman, 1975). The cilia normally beat in a rhythmic fashion to propel secretions and inhaled particles towards the mouth. Various factors have been shown to inhibit ciliary motion, such as dust, high levels of oxygen or carbon dioxide, dehydration, mediators of allergic reactions, and drugs, especially those with anti-muscarinic activity. Some adrenergic agonists have been reported to increase ciliary activity (Nadel & Davis, 1977).

Most airway secretions arise from the goblet cells and bronchial glands, both of which are most numerous in the larger bronchi and disappear at the level of the bronchioles (Kleinerman, 1975; Nadel & Davis, 1977). The goblet, or secretory, cells produce mucous secretions. Both the number and activity of goblet cells increase in response to airway irritation. However, the cells have little or no nervous control (Kleinerman, 1975).

The bronchial glands lie deeper in the airway wall and produce both mucous and serous secretions. These secretions reach the lumen through a glandular duct system. In contrast to the goblet cells, the bronchial glands are influenced by the parasympathetic nervous system. Thus, glandular secretion is affected by changes in neural activity and, in addition, may be influenced by the administration of cholinergic drugs.

Normally airway secretions and ciliary activity are balanced to provide a protective, demulcent coating which constantly flows over the airways towards the mouth, helping to remove foreign particles and debris. If this balance is interrupted, muco-ciliary transport decreases and the airways may become engorged and thickened, thus resulting in narrowing (West, 1974a). If severe, mucous plugging may occur and the airways affected will be completely obstructed. In general, cholinergic stimulation facilitates, and cholinergic blockade slows, muco-ciliary clearance. Adrenergic agents have been shown to have either no, or variable, effects on clearance (Nadel & Davis, 1977).

In addition to the factors mentioned above, the calibre of the airways is largely determined by the influence of neural activity on airway smooth muscle. The innervation of the lungs is complex and will only be briefly reviewed. More comprehensive reviews have been published by others (Fontaine & Herrmann, 1928; Macklin, 1929; Larsell & Dow, 1933; Daly & Hebb, 1966; Widdicombe & Sterling, 1970; Nadel, 1977; Richardson, 1977, 1979; Russell, 1980).

The airways of most species are innervated by both parasympathetic and sympathetic nervous systems. Possible exceptions are the rat and the rabbit in which the presence of sympathetic innervation has been questioned (El-Bermani, McNary & Bradley, 1970; Mann, 1971). Non-adrenergic, non-cholinergic inhibitory nervous activity has also been observed in airway tissue (Coburn & Tomita, 1973; Hammarstrom & Sjostrand, 1979; Kalenberg & Satchell, 1979; Chesrown, Venugopalan, Gold & Drazen, 1980; Middendorf & Russell, 1980).

The major parasympathetic control is derived from the vagus nerves (tenth cranial nerves) and their branches. Vagal efferent fibres emerge from the jugular foramina and travel down the neck towards the thorax and abdomen (Gray, 1966). In addition to numerous branches, the nerves form the extrapulmonary plexuses on the main pulmonary artery and its two branches. The extrapulmonary plexuses are continuous with others which surround the bronchi and various pulmonary blood vessels. These intrapulmonary plexuses have been reported to contain numerous parasympathetic ganglion cells from which mostly postganglionic fibres run to the bronchi and pulmonary vessels. Afferent vagal fibres from the lungs to the central nervous system also occur but will be discussed under the section dealing with lung reflexes.

Stimulation of afferent fibres in the glossopharyngeal nerves (ninth cranial nerves) is also known to produce changes in lung function (Nadel, 1965). However, these changes are all of an indirect, reflex nature and, therefore, also will be discussed under the section on lung reflexes.

Sympathetic outflow to the lung arises from the upper four to six segments of the spinal cord. Nerves from these areas relay in the thoracic, inferior-cervical, mid-cervical and superior-cervical ganglia. Fusion of the inferior-cervical ganglia with either the first thoracic ganglion, or with the upper three and four thoracic ganglia, has been observed in some species (Daly & Hebb, 1966). The resultant fused ganglia are then referred to as the stellate ganglia. Post-ganglionic fibres pass from the ganglia to various plexuses, the bronchi and pulmonary blood vessels.

Studies on the distribution of cholinergic fibres in the lungs indicated that they penetrated into the smooth muscle layers of the airways (Daly & Hebb, 1966). Studies in which fluorescent stains were used to demonstrate sympathetic fibres in the muscle layers were inconclusive. Considerable species variations have been observed, but in general, sympathetic fibres tend to be found chiefly near pulmonary blood vessels with relatively few fibres entering muscle tissue (Meier-Sydow & Gonsior, 1978; Russell, 1980).

Although the parasympathetic and sympathetic systems have so far been discussed separately, it is important to note that considerable mingling of the two systems occurs. Simple connections between the systems may be observed high in the neck region, but the connections may be complex, particularly in the pulmonary plexuses. The interweaving becomes so complex in these regions that identification of distinct sympathetic or parasympathetic components is extremely difficult.

In spite of the complex innervation patterns and crossings between the two systems, the parasympathetic system is generally said to cause constriction of airway smooth muscle, whereas, the sympathetic system is said to cause relaxation of airway smooth muscle. Although this is the general case, exceptions have been reported in the literature (Dixon & Ransom, 1912; Binger, Gaarde & Markowitz, 1931; Petrovskaia, 1939; Hebb, 1939,1940; Olsen, Colebatch, Mebel, Nadel & Staub, 1965; Nadel, 1965; Hammarstrom & Sjostrand, 1979). These also will be considered in more detail when respiratory reflexes are discussed. The predominant neural effect is one of vagal-mediated constriction and is the major contributory factor to normal tone in airway smooth muscle (Severinghaus & Stupfel, 1955; Cabezas, Graf & Nadel, 1971; Meier-Sydow & Gonsior, 1978).

Airway smooth muscle extends from the trachea to the alveolar ducts (Miller, 1947). The muscle is arranged in a geodesic pattern and contraction therefore produces both shortening and narrowing of the airways (Widdicombe, 1963; Olsen _et al_.,1967; Widdicombe & Sterling, 1970). Various effects on pulmonary ventilation can be produced by changes in muscle tone, depending on which muscles are involved. These effects can be used to divide the airways into two relatively distinct groups (Mead & Whittenberger, 1953; Mead, 1961; Nadel, 1965; Collier, 1968).

The first group (see Figure 3) consists of the large or conducting airways. Generally, these extend from the trachea to the terminal bronchioles and comprise what is called the anatomic dead space

(Guyton, 1971a). However, it should be noted that, in humans, it is more customary to define the large airways as those with an internal diameter greater than 2 mm (West, 1974b).

The second group consists of the small or peripheral airways. These extend from the terminal bronchioles to the alveoli and are the airways involved in gas exchange.

The large airways receive their blood supply primarily from the bronchial circulation, whereas the small airways are chiefly supplied with blood from the pulmonary circulation (Guyton, 1971b). Injection of drugs into the bronchial arteries therefore tends to localize initial effects in the large airways and, similarly, pulmonary injection chiefly produces changes in the small airways (Nadel 1965; DeKock, Nadel, Zwi, Colebatch & Olsen, 1966; Dautrebande, 1970).

Changes in the calibre of the large airways primarily affect the ease with which air can flow through the lungs. These changes involve non-elastic or resistive forces and are referred to as changes in flow resistance ($R_L$) or its reciprocal, conductance (Mead & Whittenberger, 1953; Mead, 1961; Colebatch, 1970; Drazen & Austen, 1974).

Changes in the calibre of the small airways primarily affect the ease with which the lungs expand to hold air and are referred to as changes in lung compliance ($C_L$) or its reciprocal, elastance (Mead & Whittenberger, 1953).

Constriction of airway smooth muscle thus produces increases in $R_L$ and decreases in $C_L$, whereas relaxation causes decreases in $R_L$ and increases in $C_L$ (Karczewski & Widdicombe, 1969b; Drazen & Austen, 1974). A wide variety of drugs and other agents can produce such changes (Bouhuys, 1977; Simonsson & Svedmyr, 1978; Svedmyr & Simonsson, 1978), but as the major portion of this thesis is concerned with airway constriction, the remaining discussion will deal chiefly with airway constriction.

Drugs and other agents can produce airway constriction directly, indirectly, or by a combination of direct and indirect actions. For example, although acetylcholine is involved in some reflex effects, at least part of its effect in the airways is due to direct action on smooth muscle (Dixon & Brodie, 1903; Karczewski & Widdicombe, 1969b). Other cholinergic agonists have been shown to produce similar effects (Dixon & Brodie, 1903; Widdicombe, 1963; Bouhuys, 1977).

Histamine also possesses both direct and indirect actions. The direct effects of histamine may be either contractile or relaxant and are thought to involve two distinct histamine receptor subtypes (Chand & Eyre, 1975). Contractile effects of histamine involve $H_1$-receptors and are blocked by 'classical' or $H_1$-receptor blockers such as mepyramine (Ash & Schild, 1966; Chand & Eyre, 1975). Relaxant effects of histamine involve $H_2$-receptors and are blocked by $H_2$-antagonists such as burimamide (Black, Duncan, Durant, Ganellin & Parsons, 1972; Chand & Eyre, 1975) or cimetidine (Brimblecombe, Duncan, Durant, Ganellin, Parsons & Black, 1975). The distribution of $H_1$- and $H_2$-receptors within the lungs is variable and, in addition, shows a large interspecies variation (Eyre, 1973; Chand & Eyre, 1977; Goadby & Little, 1978; Okpako, Chand & Eyre, 1978; Chand & DeRoth, 1979).

Indirect actions resulting in airway constriction can be classified into three broad groups: the release of constricting agents, the inhibition of dilating factors, and reflex actions.

Both chemical and immunological stimuli have been shown to induce the release of various constricting agents in the lungs (Collier, 1968; Beaven, 1976a,b; Austen, 1977; Lichtenstein, 1977; Piper, 1977; Fantozzi, Moroni, Masini, Blandina & Mannaioni, 1978). Of these factors, histamine is most directly related to the work reported in this thesis and therefore will be discussed further.

In the lungs, histamine is found chiefly in the mast cells, but also in basophils and platelets. Mast cells are found throughout the lungs, but most are found in the perivascular and peribronchial connective tissues (Kleinerman, 1975; Beaven, 1976a; Cutz & Orange, 1977). Recent studies in dogs and monkeys suggest that the number of mast cells increases as airway size decreases (Nisam, Zbinden, Chesrown, Barnett & Gold, 1978; Guerzon, Pare, Michoud & Hogg, 1979).

One of the more important stimuli for the release of histamine is the interaction between mast cells and immunoglobulin E (IgE) antibodies (Ishizaka, 1975; Austen, Lewis, Wasserman & Goetzl, 1975; Lichtenstein, 1977).

In vivo and in vitro both adrenergic and cholinergic drugs influence the release of histamine (Beaven, 1976a,b; Webb-Johnson & Andrews, 1977a,b; Austen, 1978; Wilson & McPhillips, 1978). In general, adrenergic stimulation decreases, whereas cholinergic stimulation increases the release of histamine, both effects probably involving alterations in the levels of cAMP and cGMP. However, adrenaline has been shown to facilitate the release of histamine, particularly in vivo (Fantozzi et al., 1978). According to studies with murine neoplastic mast cells, this effect most likely involves alpha-adrenergic receptors (Moroni, Fantozzi, Masini & Mannaioni, 1977).

However, data concerning the existence of alpha-receptors in airway smooth muscle is controversial (Foster, 1966; Guirgis & McNeill, 1969; Fleisch, Maling & Brodie, 1970; Simonsson, Svedmyr, Skoogh, Andersson & Bergh, 1972; Bianco, Griffin, Kamburoff & Prime, 1974; Patel & Kerr, 1975; Nousiainen, Arnala, Airaksinen & Kokkola, 1977).

Neural activity and prostaglandins have also been reported to modulate histamine release by affecting levels of cAMP and cGMP (Fantozzi et al.,1977; Austen, 1978; Webb-Johnson, 1977b). Relaxant prostaglandins and sympathetic stimulation tend to decrease the release of histamine. Contractile prostaglandins and parasympathetic stimulation tend to increase the release of histamine.

It should be noted that the agents discussed above all have actions on airway smooth muscle that are independent of any modulating effects they may exert on the release of histamine.

Agents which inhibit dilating factors may also result in airway constriction. Although vagal effects predominate in the lungs, normal bronchial tone is the net result of both constricting and dilating factors. The major dilating or relaxant influence is sympathetic, with circulating catecholamines probably being more important than neural activity (Webb-Johnson & Andrews, 1977a; Meier-Sydow & Gonsior, 1978). The relaxant effects are mediated by beta$_2$-receptors (Lands, Luduena & Buzzo, 1967).

Szentivanyi (1968) suggested that a partial blockade of beta$_2$-receptors would compromise the ability of the airways to counterbalance constricting factors. He postulated that such a blockade was inherent in the airways of asthmatic patients and that it explained the characteristic hyperreactivity of airways in this group.

Similarly, unopposed constricting forces have been suggested to explain bronchospasm and airway hyperreactivity induced by beta-receptor blocking drugs (Dollery, Paterson & Connoly, 1969). However, the unmasking of alpha-receptor activity or local anesthetic effects of the beta-receptor blockers have also been implicated (Dollery et al.,1969; Burden, Parkes & Gardiner, 1971; Simonsson et al., 1972). More recently, Maclagan & Ney (1977, 1979a,b) have reported that propranolol-induced bronchospasm could be blocked with sodium cromoglycate but was unaffected by atropine, mepyramine, cimetidine, methysergide, phenoxybenzamine or the choice of anesthetic.

Thus, although blockade of normal dilating factors seems sufficient cause for increases in muscle tone and responsiveness induced by agents such as propranolol, the actual mechanism is probably much more complex.

Various nervous reflexes (see Figure 4) are involved in the regulation of lung function (Dawes & Comroe Jr., 1954; Aviado Jr. & Schmidt, 1955; Widdicombe, 1961, 1963; Guz, Noble, Trenchard, Cochrane & Makey, 1964; Guz, Noble, Trenchard, Widdicombe, Mushin & Makey, 1966; Paintal, 1977a,b; Sampson, 1977; Richardson, 1977, 1979). Several reflexes of this type with afferent pathways mediated by fibres in the vagus nerves have been identified and will be described next.

Pulmonary stretch receptors are thought to lie in the smooth muscle layers, particularly in the large airways (Widdicombe, 1961; Guyton, 1971a; Meier-Sydow & Gonsior, 1978). Lung distension stimulates the stretch receptors and initiates the Hering-Breuer inflation reflex. This reflex causes a decrease in the frequency and force of inspiration. Subsequent lack of stretch receptor activity or lung deflation initiates the Hering-Breuer deflation reflex which causes an increase in the frequency and force of inspirations. The inflation reflex seems to be the more important and may also cause a slight degree of bronchodilation.

Lung deflation or local edema stimulates type-J receptors (Paintal, 1977a,b). These receptors are found near the alveoli and are also referred to as juxtapulmonary capillary receptors, deflation receptors or non-myelinated afferent C-fibres. Stimulation of these receptors produces apnea followed by rapid, shallow breathing, and bronchoconstriction.

Irritant receptors are found in the trachea and large bronchi (Miller, 1937; Nadel, 1965; Sellick & Widdicombe, 1969) and are often referred to as rapidly adapting or 'cough' receptors. Stimulation of these receptors follows contact with dusts or other irritants and also produces reflex bronchoconstriction.

Stimulation of chemoreceptors in the aortic arch and various other cardiopulmonary receptors which primarily mediate cardiovascular effects can also produce reflex bronchoconstriction (Dawes & Comroe Jr., 1954).

Generally vagal fibres also are thought to provide the efferent pathway for all of the reflexes described above (Dawes & Comroe Jr., 1954; Widdicombe, 1963; Nadel, 1965; Sellick & Widdicombe, 1969; Guz, Noble, Eisele & Trenchard, 1970). Reflex constriction involving vagal efferent fibres chiefly affects the large airways and can be blocked by vagotomy or atropine (Nadel, 1965; Nadel, Corn, Zwi, Flesch & Graf, 1967).

Stimulation of chemoreceptors in the carotid body and baroreceptors in the carotid sinus also produces reflex effects in the lungs.

These will be discussed in some detail as they are important to the major subject of this thesis.

Many authors have investigated and reviewed the anatomy and physiology of these structures (eg., Gerard & Billingsley, 1923; Boyd, 1937; Tchibukmacher, 1938; Eisele & Jain, 1971; Biscoe, 1971, 1977; McDonald, 1977). In addition, the extensive anatomical review by Ask-Upmark (1935) provides the basis of the anatomy described here.

Both the carotid body and the carotid sinus are found near the bifurcation of the common carotid artery (see Figure 5). The carotid body is chiefly supplied with blood from either the external carotid or occipital arteries and primarily exhibits a sensory function involving chemoreceptors.

The carotid sinus appears as a dilation of the internal carotid artery occurring at either its origin from the common carotid artery or at the origin of the occipital artery, and primarily exhibits a sensory function involving 'pressure' or baroreceptors.

These structures are generally thought to be innervated by fibres of the glossopharyngeal nerves, the vagus nerves, the cervical sympathetic nerves, and possibly the hypoglossal nerves. The most important and consistent of these is glossopharyngeal innervation. In particular, afferent fibres from both the carotid sinus and the carotid body form the carotid sinus branch of the glossopharyngeal nerve. This branch is variously referred to as the carotid sinus nerve, sinus nerve of Hering, Hering's nerve or the ramus caroticus glossopharyngei. Various connections have been observed among the carotid sinus nerves and the other nerves mentioned.

Changes in the frequency of respiration have been reported

(Ask-Upmark, 1935) and, in addition, bronchoconstriction may be a feature of respiratory reflexes mediated by afferent fibres in the glossopharyngeal nerves (Nadel, 1965). As a result, surgical procedures involving the carotid bodies and carotid sinuses have been tried in the treatment of intractable lung diseases such as asthma.

Both unilateral (Nakayama, 1961; Overholt, 1962) and bilateral (Keim, 1964; Wood, Frankland & Eastcott, 1965; Takino & Takino, 1965) removal of the carotid bodies was promoted during the 1960's. Some surgeons limited their procedure to removal of the carotid bodies (Nakayama, 1961) whereas others also removed surrounding tissues and denervated the carotid sinus (Overholt, 1962; Phillips, 1966). A combination of adverse effects, especially after bilateral surgery with sinus denervation, and lack of objective improvement in controlled studies caused most surgeons to abandon the procedures (O'Rourke & O'Rourke, 1964). More recently, Winter (1980) has suggested once again that bilateral removal of the carotid bodies may provide long-term benefit to patients with intractable asthma, probably by decreasing afferent input into a bronchoconstrictor reflex system involving chemoreceptors. This suggestion will be mentioned again in Chapter 4.

The efferent pathways of bronchoconstrictor reflexes initiated by carotid chemoreceptors or baroreceptors are not well defined, and both vagal and sympathetic pathways have been implicated.

Most investigations of possible vagal pathways have involved either vagotomy or pretreatment with atropine. In these investigations, both treatments were either without effect on reflexes with glossopharyngeal afferent pathways (Neil, Redwood & Schweitzer, 1949; Heymans, Hyde, Terp & de Vleeschhouwer, 1952; Page, 1952; Konzett, 1956; Balzer, Greeff & Westermann, 1956; D'Silva, Gill & Mendel, 1966; Daly, Korner, Angell-James & Oliver, 1978; Advenier, Boissier, Ho, Mallard & Ruff, 1978) or had inconsistent effects (Binger et al., 1931; Banister, Fegler & Hebb, 1949; Mott & Paintal, 1953; Douglas & Toh, 1953; Comroe Jr., van Lingen, Stroud & Roncoroni,, 1953; Green & Widdicombe, 1966).

The results of investigations of possible sympathetic pathways were less contradictory than the experiments with atropine or vagotomy.

Green & Widdicombe (1966) used bilateral sympathectomy to virtually eliminate bronchoconstriction induced by chemoreceptor stimulation. The sympathectomy consisted of either ligating the sympathetic nerve trunks and branches of the stellate ganglia, or removing the stellate ganglia plus the upper thoracic ganglia. Either stellectomy or sectioning of the cord has also been observed to suppress reflex respiratory responses by others (Cromer, Young & Ivy, 1933; Banister, et al., 1949; Coote & Macleod, 1974).

Nadel & Widdicombe (1963) concluded that the efferent pathways of reflexes involving both carotid baroreceptors and carotid chemoreceptors were mediated by the vagus nerves in the dog and the cat. However, their conclusions were based on experiments in which the vago-sympathetic nerves were cooled. Others have shown that stimulation of glossopharyngeal afferents produces changes in sympathetic outflow (Chien, 1967; Alanis, Defillo & Gordon, 1968; Coote & Macleod, 1974; Kezdi & Geller, 1968; DeGroat & Lalley, 1974) which could be affected by cooling (Dixon & Ransom, 1912; Daly & Mount, 1951; Nadel & Widdicombe, 1962). In particular, myelinated baroreceptor afferents are thought to be mediated centrally in the tractus solitarius nucleus and then to synapse with sympathetic fibres (Kezdi & Geller, 1968; Hilton, 1975; Spyer, 1975).

In contrast to the above workers, McCubbin, Green, Salmoiraghi & Page (1956) obtained prominent respiratory responses after vagotomy or sectioning of the cord at the 6th cervical vertebra. However, they did not distinguish between reflex and direct effects.

Other workers investigated possible pathways by sectioning and then stimulating the cut ends of individual nerves. Unfortunately the results of these investigations were often inconsistent or contradictory (see Table 1). Several factors may have contributed to the differences in results obtained by various workers:

1) Species differences have been noted in both the anatomy and innervation of the lungs, the carotid sinus, and the carotid body (Miller, 1937; Ask-Upmark, 1935).

2) In the case of the vagus or nerves from the stellate ganglia, both constricting and dilating fibres may be stimulated (Roy & Brown, 1885; Dixon & Brodie, 1903; Binger et al., 1931; Hammarstrom & Sjostrand, 1979).

3) Experiments in which the carotid sinus nerves are stimulated may be complicated by the communication of the glossopharyngeal nerves with branches of the vagus and sympathetic nerves (Gerard & Billingsley, 1923; Ask-Upmark, 1935; Boyd, 1937; Tchibukmacher, 1938; Sheehan, Mulholland & Shafiroff, 1941; Abraham, 1968; Biscoe, 1971). The methods of stimulation in various experiments were also different. In addition to electrical stimulation of nerves, known pressure changes, hemorrhage, chemicals and drugs have all been used to stimulate the appropriate receptors. Also, methods used to assess respiratory response usually differed.

4) The choice and dose of anesthetic agent can also influ-

ence respiratory responses (Douglas et al., 1950; Dawes & Mott, 1950; Douglas, Dennis, Ridgway & Bouhuys, 1969; Advenier et al., 1978).

5) The investigation of a particular reflex effect may be complicated by other reflexes or direct effects (Dawes, Mott & Widdicombe, 1951; Comroe Jr. et al., 1953; Paintal, 1955,1957; Alanis et al., 1968; Mills, Sellick & Widdicombe, 1969; Sellick & Widdicombe, 1969; Biscoe & Sampson, 1970). For example, Schneider & Yonkman (1953a,b) suggested that vagal reflexes masked the direct actions of 5HT on the heart. Thus, it seems possible that reflex effects mediated by sympathetic efferent pathways could be masked or modified by vagally-mediated changes in the pattern of breathing or other vagal reflexes.

6) Finally, many of the inconsistencies can be attributed to the different responses of spontaneously breathing and paralyzed animals. Spontaneously breathing animals chiefly experience changes in the rate and depth of breathing which may mask or alter other effects on the airways (Mead & Whittenberger, 1953; Bevan & Verity, 1961; Green & Widdicombe, 1966; Karczewski & Widdicombe, 1969a,b; Sellick & Widdicombe, 1970).

Airway constriction can also result from a combination of direct and indirect effects. For example, in addition to the direct effects discussed above, histamine has been reported to produce reflex bronchoconstriction mediated by the vagus nerves (DeKock et al., 1966; Nadel et al., 1967; Collier, 1968; James, 1969; Karczewski & Widdicombe, 1969a,b; Mills & Widdicombe, 1970; Douglas, Dennis, Ridgway & Bouhuys, 1973).

Hypercapnia has been reported to produce reflex bronchoconstriction mediated by afferent glossopharyngeal and efferent vagal fibres (Nadel & Widdicombe, 1962; Nadel, 1965; Nadel et al.,1967). Also, direct actions of carbon dioxide in the airways have been reported to produce both relaxant (Duckles, Rayner & Nadel, 1974) and contractile (Greene & Widdicombe, 1966) responses.

Because of the many species differences observed in lung structure and neural regulation of airway smooth muscle, the reasons for choosing the guinea-pig as the experimental animal used in the experiments reported in this thesis will be briefly outlined.

Historically, the guinea-pig has been the species most often used for evaluating the actions of agents on airway smooth muscle (Mills & Widdicombe, 1970). The guinea-pig is particularly suitable for studying the effects of bronchoconstrictors as smooth muscle in the airways extends into the alveolar ducts and is more abundant than in other species (Miller, 1937).

The innervation of guinea-pig lung includes parasympathetic, sympathetic, and 'purinergic' fibres and is reported to be similar to the innervation found in human lungs (Richardson, 1979; Zorychta & Richardson, 1980).

Lastly, the sensitivity of guinea-pig airways to bronchoconstrictors and bronchodilators is also similar to that in human airways (Hawkins & Schild, 1951; McDougal & West, 1953).

Both functional and morphological techniques have been developed to examine effects occurring in the large and the small airways. The methodology used for the investigations reported in this thesis is of the functional type. Therefore the principles of these methods plus those of other functional techniques used to study the actions of drugs and other agents in the airways of small animals will be briefly reviewed. These techniques can be divided into four groups:

1) Subtractor methods,
2) Plethysmographic methods,
3) Forced-oscillation methods, and
4) Interrupter methods.

The subtractor methods are based on the separation of the total transpleural pressure into two components. The first component is associated with elastic forces within the lungs, and the second is associated with resistive forces ($P_R$) which are only present during times of airflow. The methods differ chiefly in the ways used to determine $P_R$, with electrical methods being most popular (Hahn & Nadel, 1979).

The electrical methods are based on the technique described by Mead & Whittenberger (1953) and require the measurements of the volume of air flowing in the airways (V), the rate at which it flows ($\dot{V}$), and the changes in transpleural pressure associated with the changes in V and $\dot{V}$. Pulmonary compliance ($C_L$) is calculated as the slope of the pressure-volume curve obtained for times of zero airflow. When measurements are taken during respiration cycles, this parameter is referred to as dynamic $C_L$.

Pulmonary flow resistance ($R_L$) is similarly calculated from a plot of $\dot{V}$ against pressure. However, before the calculation is done, the component of pressure which is due to compliance effects must be subtracted from the total transpleural pressure. The value of $R_L$ is then calculated as 1/slope of the resultant linear plot.

Constriction of the large airways is indicated by increases in $R_L$. Even a small amount of constriction is able to produce measurable responses, as $R_L$ increases in relation to $1/r^4$, where 'r' represents the radius of the airway (West, 1974b).

Decreases in $C_L$ may be caused by pulmonary edema or muscle constriction in the small airways (Guyton, 1971b). However, as changes in $C_L$ measured in these investigations occurred promptly after drug injection and were easily reversed, muscle constriction was assumed to be the major cause of the responses (Douglas et al.,1973; Nadel & Widdicombe, 1962).

The measurement of $C_L$ and $R_L$ by the electrical subtractor method will be considered in more detail in Chapter 2 as this type of technique was used in the investigations reported in this thesis.

Plethysmographic methods are based on Boyle's Law which states that 'pressure x volume' remains constant if the temperature remains constant (West, 1974b). Essentially, animals are placed in an airtight chamber or 'pressure box' and breath against a closed air source. Chamber pressure, mouth pressure (i.e., pressure at airways opening), volume changes, and sometimes flow rate are measured. Either total lung volume or airways resistance can then be calculated. Plethysmographic techniques have been used with either spontaneously breathing or paralyzed animals.

Forced-oscillation techniques have also been used to measure $R_L$. Pressure and flow are caused to oscillate in a sinusoidal pattern, and the oscillations are then superimposed on the normal pattern of ventilation (Gold, Kessler & Yu, 1972; Hahn & Nadel, 1979). Usually this type of method measures total pulmonary $R_L$, but modifications have been developed to account for elastic, tissue and chest wall influences. These modifications make it possible to obtain measurements of lung $R_L$ (Hahn & Nadel, 1979).

Interrupter methods are based on the technique described by von

Neergaarde & Wirz (1927) and also measure pulmonary $R_L$. Mouth pressure is measured before and after a brief interruption in flow, and the pressure change is then used to determine $R_L$. The technique is more commonly used in humans (Shephard, 1959) but has been used in small animals (Schlesinger, Zeccardi & Monahan, 1980).

It should be noted that some techniques use various combinations of the four methods described above, and that computers have been employed with most of the techniques in order to increase reliability and precision of measurements. The interrupter methods are generally thought to be the least sensitive, with the other three techniques having similar sensitivities (Frank, Mead & Whittenberger, 1971; Bergman & Waltemath, 1974; Hahn & Nadel, 1979).

Lastly, before methodology is described, the known respiratory effects of the two drugs, diazoxide and serotonin (5HT), examined in these investigations will be reviewed.

Diazoxide is a benzothiadiazine derivative usually used intravenously in the treatment of hypertensive crises (Rubin, Roth, Taylor, & Rosenkilde, 1962; Speight & Avery, 1971) but also used orally in the treatment of hypoglycemic disorders (Weyer, 1968).

Diazoxide has been reported to inhibit phosphodiesterase (Moore, 1968) and to release catecholamines (Loubatieres, Mariani & Alric, 1968). A review of the literature also revealed that some patients commented on 'easier breathing' after receiving diazoxide (Just & Stein, 1969). These observations suggest that diazoxide might have bronchodilator activity.

On the other hand, the manufacturer's insert lists 'dyspnea' and 'choking sensation' as 'uncommon, reactions of doubtful relation to diazoxide.' A more 'frequent but less adverse reaction' to diazoxide is described as 'non-anginal tightness of the chest.' These observations suggest a possible bronchoconstricting action of diazoxide.

These conflicting suggestions were partially explained by work reported recently (Peterson, 1978). Using isolated guinea-pig tracheal ring preparations, diazoxide was observed to produce a small contraction before tissue relaxation. Initial, dose-related increases in total lung resistance *in vivo* were also observed using an air-overflow technique.

The increases in total lung resistance were shown to consist of marked increases in $R_L$ and smaller decreases in $C_L$. Increases in $R_L$ were selectively abolished by treatment with mepyramine (0.1 mg/kg), whereas pretreatment with either indomethacin (0.1 mg/kg) or acetylsalicylic acid selectively abolished diazoxide-induced decreases in $C_L$. Neither atropine (0.05 mg/kg) nor bilateral vagotomy affected diazoxide-induced airway constriction. Thus, it was concluded that diazoxide initially constricted and then relaxed airway smooth muscle.

The respiratory responses to 5HT have been examined *in vitro* and *in vivo*, and can be divided into those which arise from direct actions on airway smooth muscle and those which are due to indirect or reflex actions. Both types of responses have been shown to vary greatly among species (Schneider & Yonkman, 1954; Dawes *et al*., 1951; Banister *et al*., 1949; Teitelbaum & Ries, 1935).

The airways of the guinea-pig, cat and rat are the most sensitive to the direct actions of 5HT and respond with a more pronouced constriction than those of the dog (Herxheimer, 1953; Michelson, Hollander & Lowell, 1958; Jankala & Virtama, 1961; Erspamer, 1966a). In contrast, medium-sized bronchioles from rabbit and man were observed to relax when exposed to high doses of 5HT (Brocklehurst, 1958).

The reflex actions of 5HT on the airways involve several types of receptors. Type J, irritant and cardiopulmonary receptors are stimulated directly by 5HT (Comroe Jr. et al., 1953; Dawes & Comroe Jr., 1954; Paintal, 1955, 1957, 1973, 1977a). In addition, 5HT has been observed to produce localized edema (Erspamer, 1966a,b) which has been shown to be a physiological stimulant of the J-receptors (Paintal, 1955). Similarly, 5HT has been observed to stimulate pulmonary stretch receptors directly and indirectly (Schneider & Yonkman, 1954, 1953a; Paintal, 1973). Chemoreceptors in both the aortic arch and the carotid body respond to 5HT (Daly & Schweitzer, 1951; Ginzel & Kottegoda, 1954; Heymans, 1955; Bevan & Verity, 1961). Stimulation of baroreceptors in the carotid sinus by 5HT has also been reported (Heymans & Van den Heuvel-Heymans, 1950; Ginzel & Kottegoda, 1954; Ginzel, 1957).

Injection of 5HT was also observed to produce bronchoconstriction mediated by afferent fibres in the glossopharyngeal nerves of the guinea-pig (Biggs & Peterson, 1979).

The investigations reported in this thesis were undertaken to examine the effects of diazoxide and 5HT on the airways of the guinea-pig more fully, and to determine the mechanisms of action of these effects.

# CHAPTER 2

# METHODS AND MATERIALS

The drugs used in these experiments were either used as the manufacturer supplies them (eg., diazoxide injection) or were dissolved in normal saline. A list of the drugs used is provided in Appendix 1.

The methods used in the experiments have been divided into eight groups of procedures which will be discussed separately. The eight groups are:

1) Procedures for animal preparation,
2) Procedures to determine $R_L$,
3) Procedures to determine $C_L$,
4) Procedures to measure blood pressure,
5) Procedures for nerve section,
6) Procedures for carotid sinus nerve stimulation,
7) Procedures for decentralization, and
8) Procedures for statistical analysis.

## ANIMAL PREPARATION

Guinea-pigs of either sex, weighing between 400 - 1000 g, were anesthetized with urethane (1.25 -1.75 g/kg) given intraperitoneally. Early work was done with random bred animals, but later work, including all of the 'nerve stimulation' experiments, was done with Hartley strain animals.

The trachea was cannulated and connected to a Harvard Small Animal Respiration Pump set to a constant rate of 20 RPM (see Figure 6). Initially, a Fleisch pneumotach No. 0.707 was placed between the pump and the tracheal cannula, and was connected to a Grass Volumetric Pressure Transducer Model PT5 A. The signal from this transducer provided a measure of flow rate ($\dot{V}$) and was also electronically integrated to provide a volume signal (V). A side-arm of the tracheal cannula was used to monitor intratracheal pressure and was connected to a Statham P23Bb Pressure Transducer. The signal from this transducer ($P_T$) provided an estimate of the transpleural pressure. Later the Statham transducer was changed to a Grass Volumetric Pressure Transducer Model PT5 A and the pneumotach was changed to a No. 000.

Before measuring either $R_L$ or $C_L$, appropriate pairs of signals ($V$ and $P_T$ or $\dot{V}$ and $P_T$) were displayed simultaneously on an oscilloscope in order to ensure that measurements were not distorted by phase lags between signals.

All drugs used in an experiment were injected through a cannula inserted into a jugular vein. The left jugular vein was used in animals in which the right carotid sinus nerve was stimulated. Whenever possible the drugs were injected in volumes less than 0.5 ml. The cannula, which had a dead space of about 0.1 ml, was flushed with an additional 0.2 ml of normal saline after each injection. Except for diazoxide and propranolol, the drugs used in these investigations were dissolved in, or diluted with, normal saline. Therefore, saline injections were given in order to determine if the saline had any effect on baseline values of either $R_L$ or $C_L$. Drugs administered before the animal was anesthetized were administered intraperitoneally.

Pancuronium bromide (0.1 mg/kg) was administered at the start of each experiment in order to paralyze the respiratory muscles and eliminate any effects that changes in the pattern of breathing might have on measurements of either $R_L$ or $C_L$. Additional doses of pancuronium (0.05 mg/kg) were given as required. Pancuronium has been shown not to affect measurements of $R_L$ or $C_L$ (Peterson, 1978; Biggs & Peterson, 1980).

## DETERMINATION OF $R_L$

For the determination of $R_L$, the V and $P_T$ signals obtained over entire respiratory cycles were displayed on the y and x axes, respectively, of a Tektronix 5113 oscilloscope. The oscilloscope was equipped with Tektronix 5A22N differential amplifiers and a 5B12N Dual Time Base which was used as a differential amplifier, thus allowing the oscilloscope to be used as an x/y plotter. To calculate $R_L$, the component of $P_T$ due to compliance factors was electronically subtracted, resulting in a linear 'flow rate - pressure' plot. The value of $R_L$ was then taken as 1/slope of that plot.

Measurements of $R_L$ were made at ventilation volumes of 7.5 ml for random bred animals heavier than 450 g, 6.5 ml for random bred animals less than 450 g, and 7 ml for all Hartley strain animals. The animals were ventilated at these volumes except during measurement of $C_L$.

This technique for measuring $R_L$ and the technique for measuring $C_L$, which will be described next, actually measure total pulmonary values. However, chest factors have been assumed to remain constant and therefore changes in the pulmonary parameters were assumed to reflect changes in the lung parameters and no further distinction between them will be made.

Sample calculations and traces for determining $R_L$ are shown in Appendix 2.

## DETERMINATION OF $C_L$

For the determination of $C_L$, V and $P_T$ measurements were recorded at three pump volumes. Volumes of 5, 7.5 and 10 ml were used for random bred animals heavier than 450 g; volumes of 5, 6.5 and 9 ml were used for those less than 450 g; and volumes of 5, 7 and 9 ml were used for all Hartley strain animals.

The peak values of V and $P_T$ were plotted on the y and x axes, respectively, of a graph. The best straight line through these values was determined using linear regression analysis, and $C_L$ was computed as the slope of that line.

## MEASUREMENT OF BLOOD PRESSURE

For most experiments in which the blood pressure was monitored, a carotid artery was cannulated and connected to a Statham P23Bb transducer. The cannula was flushed with heparinized saline to avoid clotting. However, for some of the experiments the femoral artery was used in order to ensure that any damage or disruption to the carotid artery was avoided.

## NERVE SECTION

Three types of nerve section were performed, two involving vagotomies and one involving glossopharyngealotomy.

The first vagotomies performed were done in the mid-cervical region. The vagus nerves were isolated, cleared of connective tissue and severed. In the guinea-pig, the cervical-sympathetic nerve lies deeper than the vagus and thus these procedures did not represent vagosympathetic sectioning.

Vagotomies were also performed at the level of the jugular foramina. The nerves were isolated, cleared and cut as close to the point of emergence from the foramina as possible. This procedure is referred to as 'high vagotomy' in other sections of this thesis.

Similarly, the glossopharyngeal nerves were also identified at the level of the jugular foramina. The nerves were isolated, cleared and sectioned before the carotid sinus nerve branch was formed, or alternatively, the carotid sinus nerves and the main nerve branches were both severed.

## CAROTID NERVE STIMULATION

For these experiments, the right glossopharyngeal nerve was identified as it emerged from the jugular foramen. The carotid sinus nerve was then isolated, cleared and sectioned. The cut central end was drawn into a fine suction electrode filled with 0.9% saline and stimulated with square wave pulses for periods of 5 sec using a Grass S44 stimulator. Depending on the experiment, the pulse width was varied between 0.0125 and 3.2 msec with stimulation strengths of either 2 or 4 V. The frequency of stimulation was always 5 Hz.

## DECENTRALIZATION

Before decentralization, both carotid arteries were clamped in the mid-cervical region. The animals were then prepared by trephining the skull with a dental drill. The dura was incised and the brain was sectioned just above C1 with a probe. The hole in the skull was then plugged by gently packing it with cotton wool, and artificial respiration was started. The animal was left to stabilize for ten minutes before the carotid clamps were removed. Although no spontaneous breathing was detected, pancuronium was then administered in order to be consistent with the procedures used in non-decentralized animals.

## STATISTICAL ANALYSIS

A minimum of four replicates was obtained in each series of experiments. When possible the animals served as their own controls. Otherwise, experiments also were done in a minimum of four control animals. Paired or unpaired 't' tests were used, as appropriate, to examine the differences between means of the observed responses.

# CHAPTER 3

# RESULTS

Animals were prepared for measuring $R_L$ and $C_L$, as described in the last chapter, and these parameters were measured every 10 - 20 min for periods of 2 - 3 hr. The values of $R_L$ varied approximately 5% during that time, whereas values of $C_L$ fluctuated approximately 10%, with both increases and decreases being observed.

The correlation co-efficients of linear regression analysis lines, which were used in the determination of $C_L$, were examined and found to be > 0.94. It was therefore assumed that measurements were being obtained from the linear portion of the 'pressure-volume' plots.

As all drugs used in these experiments were injected intravenously and most were dissolved in, or diluted with, normal saline, the effects of intravenous injections of normal saline on baseline values of $C_L$ and $R_L$ were also examined. No significant changes in either parameter were observed after injection of either 0.5 or 1 ml of normal saline (see Table 2).

All other results will be reported under three separate sections:

A) Experiments involving 5HT,

B) Experiments involving diazoxide, and

C) Experiments involving stimulation of the carotid sinus nerves.

Because of the wide inter-animal variations in responses, figures show the results obtained in typical experiments unless otherwise indicated.

## A. EXPERIMENTS INVOLVING 5HT

The effects of 5HT on $R_L$ and $C_L$ were determined and, also, the effects of various drugs and treatments on the responses to 5HT were examined. The results of these experiments are reported under the following subgroups:

1) Effects of 5HT on $R_L$ and $C_L$,
2) Effects of methysergide,
3) Effects of muscarinic blockade,
4) Effects of combinations of methysergide and muscarinic blockers,
5) Effects of ganglionic blockade,
6) Effects of vagotomy,
7) Effects of glossopharyngealotomy,
8) Effects of decentralization,
9) Effects of mepyramine and disodium cromoglycate,
10) Effects of catecholamine depleting agents,
11) Effects of propranolol,
12) Effects of azapetine, and
13) Effects of clonidine.

### Effects of 5HT on $R_L$ and $C_L$

The injection of 5HT produced dose-related increases in $R_L$ which could be reproduced for periods of 3 - 4 hr without significant change (see Figure 7).

The effects of 5HT on $C_L$ were more variable. In this series of experiments, in which effects of 5HT were monitored for a 3 - 4 hr period, reproducible dose-related decreases in $C_L$ were observed in only one animal. In the other three animals, dose-related decreases in $C_L$ were observed, but the dose-response curves were not reproducible (see Figure 8). In some of the other series of experiments, no changes in $C_L$ were detected after 5HT was injected, and in others, the changes in $C_L$ were not dose-related.

### Effects of methysergide

Injection of the 5HT-antagonist methysergide (M), 0.5 mg/kg, reduced but did not abolish 5HT-induced increases in $R_L$ (see Figure 9). Increasing the dose of M to 1 mg/kg, produced no further inhibition. In this series of experiments, 5HT-induced changes in $C_L$ were variable and were not reproducible either before or after M was given.

Baseline values of either $R_L$ or $C_L$ were not significantly affected by M, 0.5 or 1 mg/kg, (see Table 2).

### Effects of muscarinic blockade

The injection of atropine (ATR), 0.05 mg/kg, also reduced 5HT-induced increases in $R_L$. Increasing the dose of ATR to 0.1 mg/kg did not produce a further reduction in the responses (see Figure 10).

The effects of ATR on 5HT-induced decreases in $C_L$ were variable. The injection of ATR, 0.05 mg/kg, abolished the responses in one animal and reduced the responses in two others. A second injection of ATR, 0.05 mg/kg, produced a further reduction in the responses to 5HT in only one of the two. In a fourth animal, 5HT-induced decreases in $C_L$ were enhanced after the first injection of ATR, and were reduced to their original level after the second dose of ATR.

Atropine methiodide (AMI), 0.05 mg/kg, also reduced, but did not abolish, 5HT-induced increases in $R_L$. Additional injections of either AMI, 0.05 mg/kg (see Figure 11) or ATR, 0.05 mg/kg (see Figure 12), failed to produce further inhibition.

The injections of AMI, 0.05 mg/kg, abolished 5HT-induced decreases in $C_L$ in two animals and reduced responses in two others. A second injection of AMI failed to abolish the remaining responses.

No significant changes in baseline values of $R_L$ or $C_L$ were observed after the injection of either ATR or AMI, 0.05 mg/kg (see Table 2). These doses of ATR and AMI reduce or abolish responses to methacholine (Biggs & Peterson, 1980).

### Effects of combinations of methysergide and muscarinic blockers

No 5HT-induced increases in $R_L$ could be detected in animals given both M, 1 mg/kg, and either ATR or AMI, 0.05 mg/kg (see Figures 9, 10, 13).

The 5HT-induced decreases in $C_L$ also were eliminated (6 animals) or markedly reduced (4 animals) after a combination of M and ATR or AMI had been administered.

### Effects of ganglionic blockade

After the injection of hexamethonium ($C_6$), 2 mg/kg, spontaneous breathing developed, making accurate measurements of $R_L$ and $C_L$ impossible. Therefore, a dosage of 3 mg/kg was tried. At the higher dose level, one animal died but two others still developed spontaneous breathing which was not blocked by additional pancuronium, 0.05 mg/kg.

Increasing the dosage of $C_6$ to 5 mg/kg prevented the occurrence of spontaneous breathing, and inhibition of some 5HT-induced changes in $R_L$ and $C_L$ were observed. However, animals given this dose of $C_6$ died before dose-response curves to 5HT could be obtained. No further experiments with $C_6$ were attempted.

Increases in $R_L$ caused by 5HT were unaffected in three animals, but reduced in four others given trimethaphan (TRI), 0.5 mg/kg. Injection of TRI, 1 mg/kg, consistently reduced 5HT-induced increases in $R_L$, however, increasing the dose to 1.5 mg/kg failed to cause additional inhibition (see Figure 14).

The 5HT-induced decreases in $C_L$ were unaffected in two animals, reduced in four animals and enhanced in one animal after the injection of TRI, 0.5 mg/kg. A similar variety of effects was observed in animals given additional injections of TRI.

Inhibition of 5HT-induced increases in $R_L$ by ATR, 0.05 mg/kg, could no longer be detected after animals had been given TRI, 1 mg/kg (see Figure 15). In addition, after animals had been given TRI, 1 mg/kg, the administration of M, 1 mg/kg, abolished the responses to 5HT whether or not the animals had been treated with ATR, 0.05 mg/kg (see Figures 14, 15).

No significant changes in either $R_L$ or $C_L$ were observed when TRI, 0.5 or 1 mg/kg, was injected (see Table 2).

### Effects of vagotomy

The 5HT-induced increases in $R_L$ and decreases in $C_L$ were not significantly changed in five animals (see Figure 16), were enhanced in one animal and reduced in another after bilateral, mid-cervical vagotomy.

Bilateral, high vagotomy also failed to significantly affect 5HT-induced increases in $R_L$ (see Figure 17). After this treatment, both enhanced and reduced decreases in $C_L$ were observed in three animals, only enhanced responses were observed in one and responses were not significantly affected in another.

Unilateral, high vagotomy also failed to significantly affect 5HT-induced increases in $R_L$. Inconsistent effects on 5HT-induced decreases in $C_L$ were observed after unilateral, high vagotomy.

As in non-vagotomised animals, combinations of M and ATR were required to eliminate the 5HT-induced increases in $R_L$.

No significant changes in either $R_L$ or $C_L$ were produced by unilateral or bilateral, high vagotomy or bilateral, mid-cervical vagotomy (see Table 2).

### Effects of glossopharyngealotomy

Bilateral glossopharyngealotomy consistently reduced 5HT-induced increases in $R_L$ (see Figure 18). The effects of glossopharyngealotomy on 5HT-induced decreases in $C_L$ were variable. These responses were not significantly changed in four animals, were inhibited in five animals, and both enhanced and reduced in one.

After bilateral glossopharyngealotomy, ATR, 0.05 mg/kg, failed to inhibit 5HT-induced increases in $R_L$, whereas, M, 1 mg/kg, abolished the responses (see Figures 18,19). Similarly, after unilateral glossopharyngealotomy, M, 1 mg/kg, alone was able to abolish 5HT-induced increases in $R_L$ (see Figure 20).

Unilateral or bilateral sectioning of the glossopharyngeal nerves produced no significant changes in baseline values of $R_L$ or $C_L$ (see Table 2).

### Effects of decentralization

The 5HT-induced increases in $R_L$ in decentralized animals were abolished by treatment with M, 1 mg/kg, alone. In two animals, M, 1 mg/kg, also eliminated 5HT-induced decreases in $C_L$. The decreases in $C_L$ were markedly reduced in two others.

In contrast, ATR, 0.05 mg/kg, consistently enhanced 5HT-induced increases in $R_L$ observed in decentralized animals. Enhanced 5HT-induced decreases in $C_L$ were also observed in three animals. Reduced decreases in $C_L$ were observed in one decentralized animal given ATR, 0.05 mg/kg.

Baseline values of $R_L$ and $C_L$ observed in decentralized animals were not significantly different from the values of $R_L$ and $C_L$ observed in normal animals (see Table 3).

### Effects of mepyramine and disodium cromoglycate

Neither mepyramine (MEP), 0.1 mg/kg, nor disodium cromoglycate (DSCG), 10 mg/kg, produced significant effects on the 5HT-induced changes in $R_L$ or $C_L$ (see Figures 21,22), or on baseline values of either parameter (see Table 2). However, this dose of MEP significantly reduces responses to histamine (Biggs & Peterson, 1980).

### Effects of catecholamine depleting agents

The possibility of sympathetic involvement in the effects of 5HT was investigated using 6-hydroxydopamine (6HD), reserpine (RES), and bretylium (BRE). Both RES and 6HD were administered 24 hr before experiments were performed, whereas BRE was administered during the experiments. In animals pretreated with either RES, 2.5 mg/kg, or 6HD, 35 mg/kg, the injection of M, 1 mg/kg, abolished 5HT-induced changes in $R_L$ and $C_L$, whereas ATR, 0.05 mg/kg, did not significantly affect 5HT-induced increases in $R_L$ (see Figures 23-26).

No changes in $C_L$ were detected in three animals pretreated with 6HD. The 5HT-induced decreases in $C_L$ observed in a fourth animal were eliminated by the injection of ATR, 0.05 mg/kg. No decreases in $C_L$ were detected in one animal pretreated with RES. ATR, 0.05 mg/kg, produced no significant effects on the 5HT-induced decreases in $C_L$ observed in another three.

Sympathectomy was judged to be incomplete in animals pretreated with 6HD as increases in blood pressure were observed in these animals after the injection of tyramine, 0.5 or 1 mg/kg. In contrast, blood pressure responses to tyramine, 0.5 or 1 mg/kg, were absent or just barely detectable in animals pretreated with RES.

The 5HT-induced increases in $R_L$ were reduced by BRE, 7.5 mg/kg (see Figures 27, 28). The same dose of BRE produced variable effects on 5HT-induced decreases in $C_L$. Reduced, enhanced, or both reduced and enhanced responses were observed in six animals. No significant changes in the responses were observed in one animal. No 5HT-induced decreases in $C_L$ were detected in three other animals treated with BRE.

Injection of ATR, 0.05 mg/kg, produced no significant changes in 5HT-induced increases in $R_L$ after animals had been given BRE (see Figure 27). After injection of ATR, the 5HT-induced decreases in $C_L$ were enhanced in one animal, but no significant effects were observed in another. No decreases in $C_L$ were detected in two other animals.

In contrast, M, 1 mg/kg, abolished 5HT-induced changes in $R_L$ and

$C_L$ in animals treated with BRE (see Figure 28). These responses were also abolished in three animals given both M and ATR (see Figure 27). In another animal, the increases in $R_L$ were abolished, but the decreases in $C_L$ were enhanced.

Dexamphetamine (DEX), 5 mg/kg, partially reversed the blockade of 5HT-induced increases in $R_L$ in three animals approximately 15 min after injection (see Figures 27, 28). In another four animals which also were given ATR, 0.05 mg/kg, the reversal of the blockade was not detected 30 min after injection of DEX, 5 mg/kg.

Blood pressure responses to tyramine, 0.5 or 1 mg/kg, although reduced from control values, could be obtained after BRE, 7.5 or 15 mg/kg, had been administered.

Baseline values of $R_L$ and $C_L$ in pretreated animals were not significantly different from values obtained in normal animals (see Table 3). Similarly, administration of BRE, 7.5 or 15 mg/kg, during the experiments also failed to produce significant changes in $R_L$ or $C_L$ (see Table 2). Administration of DEX, 5 mg/kg, also failed to affect the baseline values of either $R_L$ or $C_L$ (see Table 2).

### Effects of propranolol

Propranolol (PRO), 1 mg/kg, consistently increased 5HT-induced increases in $R_L$ (see Figure 29), but produced inconsistent effects on 5HT-induced decreases in $C_L$.

No significant changes in $R_L$ or $C_L$ were observed after administration of PRO, 1 mg/kg (see Table 2).

### Effects of azapetine

Azapetine (AZP), 0.5 mg/kg, consistently inhibited 5HT-induced increases in $R_L$ (see Figure 30). The 5HT-induced decreases in $C_L$ were either reduced (2 animals) or not significantly affected (2 animals) by AZP, 0.5 mg/kg.

This dose of AZP did not produce complete alpha-adrenergic blockade as phenylephrine (PHE), 0.025 or 0.05 mg/kg, was able to cause increases in blood pressure after the AZP had been administered. No significant changes in baseline values of $R_L$ and $C_L$ were observed after PHE was injected (see Table 2). However, histamine-induced increases in $R_L$ were not significantly affected by AZP, 0.05 mg/kg (see Figure 30), and thus, AZP appeared to selectively inhibit 5HT at this dose level. When the dose of AZP was increased to 1 mg/kg, responses to both histamine and 5HT were reduced (see Figures 31, 32).

No 5HT-induced increases in $R_L$ were observed in animals given both AZP, 0.5 mg/kg, and M, 1 mg/kg (see Figure 30).

### Effects of clonidine

After injection of clonidine (CLD), 0.15 mg/kg, 5HT-induced increases in $R_L$ were enhanced in three animals (see Figure 33) and both enhanced and unchanged responses were observed in a fourth animal. No significant changes in 5HT-induced decreases in $C_L$ were observed after injection of CLD in two animals. In another, the responses were enhanced and, in a fourth, no significant changes in the responses were observed.

Injection of M, 1 mg/kg, abolished 5HT-induced increases in $R_L$ in animals that had been given CLD, 0.15 mg/kg (see Figure 33).

The administration of CLD, 0.15 mg/kg, produced no significant changes in baseline values of $C_L$, but did produce increases in the baseline values of $R_L$ (see Table 2). Baseline values of $R_L$ were recovered before subsequent doses of 5HT were tested.

## B. EXPERIMENTS INVOLVING DIAZOXIDE

Some experiments which had been reported previously (Peterson, 1978) were repeated in order to increase number of replicates. The results of these experiments were in agreement with the earlier work and therefore will be briefly summarized as in Chapter 1:

Diazoxide-induced increases in $R_L$ were selectively abolished by treatment with MEP, 0.1 mg/kg, but were not significantly affected by mid-cervical, bilateral vagotomy or treatment with ATR, 0.05 mg/kg.

Diazoxide-induced decreases in $C_L$ also were not significantly affected by mid-cervical, bilateral vagotomy or treatment with ATR, 0.05 mg/kg, but were selectively abolished by indomethacin, 0.1 mg/kg, or acetylsalicylic acid, 1 mg/kg.

Other experiments were also performed and the results are reported under subgroups similar to those in Section A. Although dose-response curves could be obtained with diazoxide (see Figures 34, 35), there was a possibility of auto-inhibition due to the relaxant effects of diazoxide on the airways (Peterson, 1978). Therefore, rather than using animals as their own controls, for these experiments the effects of diazoxide in treated and non-treated animals were compared.

### Effects of trimethaphan

No significant increases in $R_L$ were induced by diazoxide, 40 mg/kg, in animals pretreated with TRI, 0.5 or 1 mg/kg (see Figure 36). Diazoxide-induced decreases in $C_L$ were also blocked by TRI, 0.05 mg/kg.

However, no significant changes in these responses were observed in animals given TRI, 1 mg/kg.

### Effects of glossopharyngealotomy

Unilateral glossopharyngealotomy consistently reduced, but did not abolish, diazoxide-induced increases in $R_L$, but produced no significant effects on diazoxide-induced decreases in $C_L$ (see Figure 37).

Bilateral glossopharyngealotomy also failed to produce any significant changes in diazoxide-induced decreases in $C_L$. However, this treatment abolished diazoxide-induced increases in $R_L$ (see Figure 37).

### Effects of decentralization

Decentralized animals died after the injection of diazoxide, 40 mg/kg. Therefore, diazoxide, 20 mg/kg, was used for this series of experiments.

Diazoxide-induced decreases in $C_L$ observed in decentralized animals were not significantly different from those observed in normal animals, whereas diazoxide-induced increases in $R_L$ could not be detected in decentralized animals (see Figure 38).

### Effects of disodium cromoglycate

Injection of DSCG, 10 mg/kg, abolished diazoxide-induced increases in $R_L$ but had no significant effect on diazoxide-induced decreases in $C_L$ (see Figure 39). In contrast, neither 5HT- nor histamine-induced changes in $R_L$ and $C_L$ were affected by DSCG, 10 mg/kg (see Figures 22, 40).

### Effects of catecholamine depleting agents

Pretreatment with RES, 2.5 mg/kg, 24 hr before testing prevented the diazoxide-induced increases in $R_L$. Similarly, diazoxide-induced decreases in $C_L$ could not be detected in three reserpinized animals. However a normal decrease in $C_L$ was observed in one reserpinized animal given diazoxide, 40 mg/kg.

Injection of BRE, 15 mg/kg, also abolished diazoxide-induced increases in $R_L$, but did not significantly affect diazoxide-induced decreases in $C_L$ (see Figure 41).

A partial recovery of diazoxide-induced increases in $R_L$ was observed approximately 30 min after DEX, 5 mg/kg, was administered to animals that had previously been treated with BRE, 15 mg/kg. Diazoxide-induced decreases in $C_L$ were reduced in animals treated with both BRE, 15 mg/kg, and DEX, 5 mg/kg (see Figure 41).

### Effects of propranolol

Diazoxide-induced changes in $R_L$ and $C_L$ were increased by treatment with PRO, 1 mg/kg. However, the effects on the increases in $R_L$ were not statistically significant due to the large variation in responses observed.

### Effects of azapetine

Injection of AZP, 1 mg/kg, produced no significant effects on diazoxide-induced decreases in $C_L$, but consistently reduced diazoxide-induced increases in $R_L$ (see Figure 42). Diazoxide-induced increases in $R_L$ were abolished in only one animal given AZP, 1 mg/kg.

### Effects of clonidine

Diazoxide, 40 mg/kg, produced no significant changes in $R_L$ or $C_L$ in animals treated with CLD, 0.15 mg/kg (see Figure 42).

## C. EXPERIMENTS INVOLVING STIMULATION OF THE CAROTID SINUS NERVE

The effects of stimulation of the carotid sinus nerve on $R_L$ and $C_L$ were determined and, also, the effects of various drugs and treatments on the response to nerve stimulation (NS) were examined. Subgroups similar to those in the previous two sections have been used to organize the results of these experiments.

### Effects of carotid sinus nerve stimulation in normal and vagotomised animals

At either 2 or 4 V, NS produced increases in $R_L$ which were dependent on the pulse width (see Figure 43). The threshold for a response was near a pulse width of 0.0125 msec and responses reached a maximum near a pulse width of 0.2 msec in most animals. Results obtained with a stimulus strength of 2 V were always similar to those obtained with a stimulus strength of 4 V. Therefore, the results of these two groups of experiments will not be treated separately.

No significant changes were observed in $C_L$ after NS in the first seven animals tested (see Figure 44). Therefore, only changes in $R_L$ were measured in all subsequent experiments.

Bilateral, mid-cervical vagotomy had no significant effects on the responses to NS (see Figure 45). All further experiments were done in vagotomised animals.

The responses to NS were monitored for periods of approximately 2-3 hr with response-pulse duration curves being obtained every 20 min at both 2 and 4 V. No significant changes in the responses were observed (see Figure 46).

### Effects of trimethaphan

Responses to NS were consistently abolished by TRI, 0.5 mg/kg.

### Effects of decentralization

Responses to NS could not be detected in decentralized animals.

### Effects of muscarinic blockade

The injection of ATR, 0.05 mg/kg, consistently reduced, but did not abolish, the responses to NS. Additional doses of ATR failed to produce greater inhibition (see Figure 47). Similar results were obtained with AMI, 0.05 mg/kg (see Figure 48). Similarly, the injection of ATR, 0.05 mg/kg, after AMI, also failed to produce a greater degree of inhibition of the responses to NS (see Figure 49).

### Effects of mepyramine and disodium cromoglycate

The responses to NS were reduced but not abolished by MEP, 0.1 mg/kg. As with the muscarinic blockers, increasing the dose of MEP produced no further reduction in the responses to NS (see Figure 50).

Single and multiple injections of DSCG, 10 mg/kg, produced results similar to those observed with MEP (see Figure 51).

Combinations of DSCG, 10 mg/kg, and MEP, 0.1 mg/kg, were no more effective than either drug used alone (see Figure 52).

### Effects of muscarinic blockers with mepyramine or disodium cromoglycate

Combinations of DSCG, 10 mg/kg, or MEP, 0.1 mg/kg, and ATR or AMI, 0.05 mg/kg, abolished the responses to NS (see Figures 53-56). The order of administration of the drugs was unimportant to the abolition of responses.

### Effects of catecholamine depletors

The possibility of sympathetic involvement in the responses to NS was investigated using RES, 6HD, BRE and bethanidine (BET). All except RES were administered during experiments. In addition, RES and 6HD were used to pretreat animals 24 hr before experiments.

Responses to NS could not be detected in animals pretreated with RES, 2.5 mg/kg, or 6HD, 35 mg/kg, even when pulse widths as high as 3.2 msec were used. However, normal responses were obtained in animals pretreated with normal saline injections 24 hr before testing.

When 6HD was given during experiments, successive doses of 5 mg/kg were administered. As doses of 5, 10 and 15 mg/kg were reached, a progressive inhibition and then abolition of responses to NS was observed (see Figure 57). Administration of 6HD, 5 mg/kg, produced no significant changes in baseline values of $R_L$ (see Table 2).

Responses to NS were reduced by BRE, 10 mg/kg, and abolished by BRE, 15 mg/kg. Partial recovery of the responses to NS was observed 15 - 30 min after the administration of DEX, 5 mg/kg, in these animals (see Figure 58).

Similar results were obtained with BET (see Figure 59). Responses to NS were reduced by BET, 1 mg/kg, and abolished by BET, 1.5 mg/kg. Some responses to NS could again be detected in these animals 15-30 min after the adminstration of DEX, 10 mg/kg (see Figure 59).

Injection of BET, 1 or 1.5 mg/kg, produced no significant effects on baseline values of $R_L$ (see Table 2).

### Effects of clonidine

No responses to NS could be detected in animals given CLD, 0.15 mg/kg.

# CHAPTER 4

# DISCUSSION

The first experiments in these investigations were done to ensure that the parameters measured were accurate and reproducible. Measurements of both $R_L$ and $C_L$ may be influenced by changes in either the rate or depth of breathing (Mead & Whittenberger, 1953). Therefore, pancuronium bromide was administered at the start of each experiment in order to paralyze respiratory muscles and prevent any alterations in the pattern of breathing. Pancuronium has been reported to produce no significant effects on baseline values of $R_L$ or $C_L$ (Peterson, 1978; Biggs & Peterson, 1980). This muscle relaxant was chosen because of its non-depolarizing action and its long duration of action. Also, pancuronium has been shown to produce little ganglionic blockade and minimal histamine release (Koelle, 1975).

Accurate measurements of $C_L$ values, by subtractor methods, require that calculations be done using values obtained from the linear portion of the 'volume-pressure' curves (Mead & Whittenberger, 1953). Correlation co-efficients of the linear regression lines, used to calculate $C_L$ in these investigations, were always greater than 0.94 and it was therefore concluded that both control and test measurements of $C_L$ were computed using values from the linear portion of the curves.

Values of $R_L$ and $C_L$ did not vary more than 10% over periods of 2 - 3 hr. Also, these parameters were not significantly affected by the injection of normal saline in volumes as large as 1 ml. Therefore, it was concluded that changes in $R_L$ and $C_L$ detected in these experiments were due to the drugs (5HT or diazoxide) or treatment (NS) tested.

The various drugs and treatments used to investigate the responses to 5HT, diazoxide and NS, with the exception of CLD, also failed to produce significant changes in $R_L$ and $C_L$. As most of these drugs and treatments affect blood pressure, but did not significantly alter $R_L$ or $C_L$, it was assumed that the responses measured in these investigations were independent of any cardiovascular changes which may have occurred. Others have also been able to isolate respiratory responses from cardiovascular responses to the same stimulus (Dawes & Mott, 1950; Dawes, Mott & Widdicombe, 1951).

The administration of 5HT produced constriction in both the large (increases in $R_L$) and small (decreases in $C_L$) airways. However, the decreases in $C_L$ were not always reproducible and were affected in a variety of ways by any one drug or treatment examined in these investigations. Therefore, no specific mechanism could be suggested to explain the actions of 5HT in the small airways.

In contrast, the increases in $R_L$ produced by 5HT were stable and reproducible for periods of 3 - 4 hr. In addition, a specific pattern could be detected in the effects that the various other drugs and treatments produced on the responses to 5HT in the large airways. Therefore, these results will be discussed in greater detail.

Because of the known effects of 5HT in other systems (Erspamer, 1966a; Douglas, 1975), the effects of M and ATR on 5HT-induced increases in $R_L$ were examined first. The results of these experiments indicated that 5HT produced constriction in the large airways in two ways.

Firstly, constriction was produced by an action of 5HT on airway smooth muscle. Three types of receptors have been reported to mediate effects of 5HT on smooth muscle (Apperly, Humphrey & Levy, 1977). The 'D-receptors' mediate direct actions and are blocked by drugs such as dibenzyline or M, whereas 'M-receptors' mediate indirect actions involving ganglion cells and are blocked by cocaine or morphine (Douglas, 1975; Apperly et al., 1977). The third type of receptor was stimulated by M and unaffected by morphine (Apperly, et al., 1977). As 5HT-induced increases in $R_L$ were inhibited by M, it was concluded that a direct action of 5HT on smooth muscle was involved. Doubling the dose of M did not produce further inhibition and, thus, it was concluded that a second, M-resistant action was also involved.

The constriction produced by 5HT was reduced, but not abolished, by either ATR or AMI. Similarly, combinations of ATR and AMI were no more effective than either drug used alone. The M-resistant component of action was therefore thought to be muscarinic in nature. In particular, the data obtained with the quaternary compound, AMI, indicated the involvement of peripheral muscarinic receptors.

The ganglionic blocking agent TRI also reduced, but did not abolish, the 5HT-induced increases in $R_L$. However, the ATR-sensitive component of action could not be detected in animals that had been given TRI, and responses to 5HT in these animals could be eliminated by M alone. It was therefore concluded that the ATR-sensitive component of action involved a ganglionic relay.

Using $C_6$ proved unsuitable for demonstrating this ganglionic link for two reasons. First, after low doses of $C_6$ were administered, subsequent doses of 5HT produced spontaneous breathing which was resistant to additional doses of pancuronium. Second, after higher doses of $C_6$ were given, the animals died before dose-response curves to 5HT could be obtained. It is interesting to note that Dontas & Nickerson (1956) reported that ganglionic blocking agents, in doses lower than those required to suppress chemoreceptor activity, were able to stimulate carotid chemoreceptors. TRI possesed the least excitatory activity of the agents tested by Dontas & Nickerson (1956) and worked well in these investigations.

The ATR-sensitive component of action was also absent in decentralized animals, and it was assumed that this component was part of a central, autonomic reflex action of 5HT. The remaining experiments were done in order to define the afferent and efferent pathways of this reflex.

As many of the reflex effects of 5HT have been shown to involve the vagus nerves (Erspamer, 1966a,b), the effects of bilateral, mid-cervical vagotomy on 5HT-induced increases in $R_L$ were examined. However, this treatment produced no significant changes in the bronchoconstrictor responses to 5HT. If the vagus nerves were involved in the reflex actions of 5HT, the lack of effects produced by mid-cervical vagotomy could be explained by the high degree of branching of the vagus nerves (Gray, 1966). Therefore, the effects of bilateral vagotomies done at the level of the jugular foramina were also examined. High vagotomy also failed to produce significant effects on the responses to 5HT.

In addition, the ATR-sensitive component of action was still present after vagotomy, and both a muscarinic blocker and M were required to abolish 5HT-induced increases in $R_L$ in vagotomised animals. Clearly, the reflex action of 5HT was independent of the vagus nerves.

In contrast to vagotomy, bilateral glossopharyngealotomy reduced the bronchoconstrictor responses to 5HT and eliminated the ATR-sensitive component of action. Similarly, after unilateral glossopharyngealotomy, only M was required to abolish the responses to 5HT. These results suggested that fibres in the glossopharyngeal nerves provided the afferent pathway for the reflex component of action of 5HT in the airways. Other respiratory reflexes with afferent glossopharyngeal pathways have been described (Ask-Upmark, 1935; Nadel, 1965).

After pretreatment with 6HD or RES, only the M-sensitive actions of 5HT could be detected suggesting the presence of a central or peripheral adrenergic component in the efferent pathway. The ability of DEX to partially reverse a similar blockade, induced by BRE, confirmed the involvement of actions at adrenergic nerve terminals. Although sympathectomy was not complete in some of these animals, the abolition of the reflex action of 5HT may be explained by the fact that some structures are more sensitive to adrenergic depletion than others (Thoenen & Tranzer, 1968; Haeusler, 1971; Kostrzewa & Jacobowitz, 1974). In general, heart muscle and iris are thought to be highly susceptible, whereas sympathetic ganglia and adrenal glands tend to be least susceptible. Recently, McGowan & Niewoehner (1980) have demonstrated that the susceptibility of guinea-pig trachea to chemical sympathectomy is similar to that of iris and may be greater than that of heart muscle.

The 5HT-induced increases in $R_L$ were enhanced by PRO. However, PRO also markedly increased the response to diazoxide in some animals, and has been reported to potentiate histamine-induced constriction (Collier & James, 1967; Douglas & Bouhuys, 1969). Thus, the results observed were probably due to a non-specific potentiation and suggest that beta-adrenergic receptors are not involved in the responses to 5HT.

The administration of the lower dose of AZP that was tested selectively reduced the responses to 5HT. In addition, M was able to abolish the responses to 5HT in animals given AZP. These results suggest that alpha-adrenergic receptors might be involved in the reflex component of action of 5HT. With this idea in mind, it was interesting to note that PHE increased the baseline value of $R_L$ in only 1 (of 9) animal.

At present the data concerning the existence of alpha-receptors in the lungs remains inconclusive (Foster, 1966; Giurgis & McNeill, 1969; Fleisch et al.,1970; Cabezas et al.,1971; Simonsson et al., 1972; Bianco et al., 1974; Nousiainen et al., 1977). Thus, the inability of PHE to significantly affect baseline values of $R_L$ might be due to a lack of alpha-adrenergic receptors and be in conflict with the implications of the results obtained with AZP. At least two other alternative explanations might resolve this apparent conflict.

Firstly, the alpha-receptors may not be present at the level of the effector organ, that is, airway smooth muscle, but may exist elsewhere in the pathway.

Secondly, PHE may have a low affinity for the type of alpha-receptor involved in the responses to 5HT. Two types of alpha-receptors have been described, (Starke, Endo & Taube, 1975a,b; Wikberg, 1979). The $alpha_1$-receptors are chiefly located post-synaptically in smooth muscle cells, whereas $alpha_2$-receptors are chiefly located pre-synaptically in adrenergic nerve terminals (Wikberg, 1979, Melchiorre, 1980). PHE preferentially stimulates $alpha_1$-receptors and has little affinity for $alpha_2$-receptors (Wikberg, 1979). There is evidence to suggest that AZP acts at both types of alpha-receptors (Sheys & Green, 1972; Melchiorre, 1980). Thus, the apparent discrepancy between the results obtained with AZP and PHE may be explained by assuming that the effects of AZP primarily involved actions at alpha$_2$-receptors.

The results obtained with CLD support the involvement of alpha$_2$-receptors in the reflex action of 5HT. CLD has been shown to have more affinity for alpha$_2$-receptors than alpha$_1$-receptors (Wikberg, 1979) and can produce both stimulation and inhibition of the receptors (Nickerson & Ruedy, 1975). The increases in $R_L$ produced by CLD could be explained by an initial stimulation of these receptors.

Although enhanced responses to 5HT were observed after treatment with CLD, the responses could be eliminated by the injection of M. These results indicated that the direct effects of 5HT were enhanced, but that the reflex effects of 5HT were abolished, suggesting that the initial receptor stimulation was followed by inhibition.

In summary, the 5HT-induced increases in $R_L$ were due to a combination of direct and indirect actions. The indirect action involved a non-vagal, central autonomic reflex. The afferent pathway of this reflex involved afferent fibres in the glossopharyngeal nerves, whereas the efferent pathway appeared to involve alpha$_2$-adrenergic receptors.

Some preliminary experiments (Biggs & Peterson, 1979) suggested that part of the constriction produced by diazoxide also involved a non-vagal reflex component of action.

The diazoxide-induced decreases in $C_L$ observed in decentralized animals were not significantly different from those observed in normal animals. Also, the various doses of TRI produced inconsistent effects on these responses. These results, in conjunction with the pharmacological distinction between the responses of the large and small airways to diazoxide reported previously (Peterson, 1978), suggested that changes in $C_L$ did not result from a reflex action of diazoxide. Therefore, only diazoxide-induced increases in $R_L$ will be discussed further.

Either decentralization or treatment with TRI eliminated diazoxide-induced increases in $R_L$, and thus supported the idea that diazoxide also possessed a reflex component of action. However, in contrast to 5HT-induced constriction, ATR had no significant effect on diazoxide-induced constriction. Also, MEP abolished responses to diazoxide but produced no significant effect on 5HT-induced constriction.

Bilateral glossopharyngealotomy abolished the responses to diazoxide. It was therefore concluded that the afferent pathway was mediated by fibres in the glossopharyngeal nerves. Unlike the reflex actions of 5HT, the responses to diazoxide were only reduced by unilateral section of the glossopharyngeal nerves and were not eliminated.

Either DSCG or MEP abolished the responses to diazoxide in these experiments. However, responses to either 5HT or exogenous histamine were not significantly affected by DSCG. These results suggested that the diazoxide-induced increases in $R_L$ could be due to the release of histamine rather than some histaminergic action of diazoxide.

Other workers have presented evidence to show that stimulation of baroreceptors in the carotid sinus may cause the release of histamine in peripheral vascular tissues (Beck, 1965; Brody, 1966; Levin, Bartlet & Beck, 1968; Tobia, Adams, Miya & Bousquet, 1969, 1970). More recently Lee, Walsh, Mokler & Tobia (1981) have reported that, in the rat, decreases in hindlimb vascular resistance produced by electrical stimulation of the glossopharyngeal nerves could be inhibited by the antihistamine, tripelennamine, but not by ATR.

Diazoxide induced increases in $R_L$ could not be detected in animals treated with BRE or pretreated with RES. Responses smaller than those observed in normal animals were observed in animals given DEX after treatment with BRE. These results are similar to those obtained with 5HT and suggest that the efferent pathway of the reflex action of diazoxide also involves a sympathetic component. Judging by the results obtained with PRO, the diazoxide-induced increases in $R_L$, like those of 5HT, were independent of any beta-receptor involvement.

The responses to diazoxide were inhibited by both AZP and CLD, suggesting that this reflex, like the reflex initiated by 5HT, also involved alpha$_2$-receptors.

In summary, the diazoxide-induced increases in $R_L$ were, like responses to 5HT, shown to involve a non-vagal, central autonomic reflex. Afferent fibres in the glossopharyngeal nerves and an efferent pathway with a sympathetic component also seem likely for this reflex. However, in contrast to 5HT, diazoxide appeared to cause the reflex release of histamine. Also, the reflex action of diazoxide was not affected significantly by muscarinic blockade and therefore did not possess a muscarinic component of action. Although reduced after unilateral glossopharyngealotomy, the reflex effects of diazoxide, unlike those of 5HT, could be detected with only one glossopharyngeal nerve intact.

Orthodromic stimulation of the carotid sinus nerve was used to try and mimic the reflex actions of 5HT and diazoxide. No significant effects on baseline values of $C_L$ were produced by NS, thus confirming the hypothesis that changes in $C_L$ produced by either 5HT or diazoxide did not involve reflex actions mediated by glossopharyngeal nerves.

In contrast, NS produced increases in $R_L$ which were dependent on the pulse width. These responses were absent in decentralized animals and could be eliminated in normal animals by TRI, indicating that they were due to a central reflex action.

No significant changes in the responses to NS were observed after bilateral vagotomy. These results indicated that, firstly, the responses to NS were independent of the vagus nerves, and secondly, that there was no spread of the electrical stimulus despite the close proximity of the vagus and glossopharyngeal nerves at the level of the jugular foramen.

The experiments with ATR, AMI and MEP indicated that the responses to NS involved both muscarinic and histaminergic components. As the muscarinic component was blocked by AMI, it was concluded that peripheral muscarinic receptors were involved. The histaminergic component could be eliminated with either MEP or DSCG. Thus, NS produced effects which were similar to the reflex actions of both 5HT and diazoxide.

Like the drug-induced effects, the responses to NS were not detected in animals pretreated with either RES or 6HD. Similarly, increasing doses of BRE or BET reduced, and then abolished, responses to NS. Partial recovery of the responses to NS in these animals was detected after the administration of DEX. Thus, the efferent pathways of the responses to NS involved sympathetic components.

No responses to NS were detected in animals given CLD, thus suggesting the involvement of alpha$_2$-receptors.

In conclusion, it was determined that 5HT produced constriction in the large airways of the anesthetized, paralyzed guinea-pig by both direct and indirect actions. The indirect action of 5HT was shown to involve a central, autonomic reflex which was independent of the vagus nerves. Fibres of the glossopharyngeal nerves provided the afferent pathway, and the efferent pathway was shown to involve a sympathetic component.

Similarly, diazoxide-induced increases in $R_L$ were also shown to involve a central, autonomic reflex. This reflex was also mediated by afferent fibres in the glossopharyngeal nerves and involved a sympathetic component in the efferent pathway. However, two distinct reflex arcs were involved in the responses to the two drugs.

The reflex arc involved in the responses to 5HT was shown to involve peripheral muscarinic receptors which could be blocked by AMI. Although central actions seem unlikely with the low doses used in these experiments, ATR can act either centrally or peripherally, but produced no further inhibition in animals pretreated with AMI. Thus, central muscarinic receptor involvement seemed unlikely unless the receptors are part of the neuronal circuit which also involves the peripheral receptors. Based on the anatomy of the carotid body (McDonald, 1977) these receptors most likely form part of the efferent pathway.

The results of these investigations also suggested that $alpha_2$-receptors formed part of the reflex arc. However, with the available evidence, it is impossible to determine if these receptors occur before or after the muscarinic receptors in the pathway.

At first, a central location seemed likely as others have reported that afferent fibres of the glossopharyngeal nerves synapse with sympathetic fibres in the tractus solitarius nucleus (Kezdi & Geller, 1968; Hilton, 1975; Spyer, 1975). The loss of the reflex component of action of 5HT after treatment with BET and RES could then be explained by the central actions of these drugs. However, BRE and 6HD are unlikely to enter the CNS from the bloodstream, and both of these drugs also abolished the reflex actions of 5HT. Thus, a peripheral sympathetic component must be present.

The most likely peripheral sites for sympathetic involvement would be within sympathetic ganglia or at the level of the airways. Sympathectomy was judged to be incomplete in animals treated with either 6HD or BRE. Therefore, as the sympathetic ganglia tend to be the least susceptible structures to chemical sympathectomy (Thoenen & Tranzer, 1968; Haeusler, 1971; Kostrzewa & Jacobowitz, 1974) and sympathectomy was incomplete, location of the alpha$_2$-receptors in sympathetic ganglia seems unlikely.

Similarly, the involvement of alpha$_2$-receptors at the level of airway smooth muscle also seems unlikely, at first, as most alpha-receptors in smooth muscle are of the alpha$_1$-receptor subtype (Wikberg, 1979). Also, as discussed previously, the existence of alpha-receptors in the airways is still a matter of controversy. However, the actions of various alpha$_2$-agonists and antagonists have not been thoroughly examined in airway smooth muscle. Such a study might help to settle the controversy surrounding the existence of alpha-receptors in the airways.

Figure 60 depicts several reflex arcs which are consistent with the data obtained in these investigations.

The reflex arc involved in the responses to diazoxide does not have a cholinergic component, but does appear to mediate the release of histamine in the large airways. Alpha$_2$-receptor involvement has also been implicated in this reflex arc, but, as with the receptors associated with responses to 5HT, the available evidence does not indicate their location. In addition to the possible sites discussed above, the results obtained with hindlimb preparations also suggest a possible vascular location (Beck, 1965; Brody, 1966; Levin et al., 1968; Tobia et al., 1969,1970; Lee et al., 1980).

Possible reflex arcs consistent with the results obtained in experiments with diazoxide are shown in Figure 61.

As the reflexes reviewed in this thesis all involved different types of receptors, it seems reasonable to assume that the reflex effects of diazoxide and 5HT also involve the stimulation of distinct receptor types. As diazoxide is a hypotensive agent and 5HT has been shown to stimulate chemoreceptors in some species (Ginzel, 1954; Ginzel & Kottegoda, 1954) it seems possible that the drugs are affecting carotid baroreceptors and chemoreceptors, respectively. If this is the case, certain clinical implications become apparent, although care must be exercised in extrapolating from animals, and in particular from the guinea-pig, to humans.

Recently, for example, Winter (1980) has advocated bilateral removal of the carotid bodies without denervation of the carotid sinus in order to decrease afferent bronchoconstrictor input from chemoreceptors. However, in the investigations reported here, unilateral nerve section was shown to distinguish between reflex constriction produced by 5HT, or chemoreceptor stimulation, and diazoxide, or baroreceptor stimulation. In particular, only unilateral glossopharyngealotomy was required to eliminate the reflex effects of 5HT, suggesting that bilateral removal of carotid bodies, as advocated by Winter, is not required. Also, based on these results, treatment with a muscarinic antagonist would be as effective as surgery in blocking bronchoconstrictor input from chemoreceptors.

Similarly, our results suggest that DSCG would be as effective as carotid sinus denervation in blocking bronchoconstrictor input from baroreceptors. Although DSCG was initially thought only to act on mast cells (Cox and Beach, Blair, Clarke, King, Lee, Loveday, Moss, Orr, Ritchie & Sheard, 1970), more recently, others have suggested that DSCG may have additional actions either on cholinergic fibres associated with the reflex effects initiated by irritant receptor activity, or directly on airway smooth muscle (Dixon, Jackson & Richards, 1980; Harries, Parkes, Lessof & Orr, 1981).

In our experiments, responses to exogenous histamine or 5HT were not significantly affected by DSCG, thus a direct effect of DSCG resulting in a change in airway smooth muscle contractility seems unlikely. Also, in our experiments, DSCG blocked reflex bronchoconstriction which was independent of the vagus nerves and did not have a muscarinic component. Therefore, an action on cholinergic fibres is also unlikely in the guinea-pig. However, it is interesting to note that the bronchial hyperreactivity induced by sulphur dioxide in asthmatics was inhibited by DSCG, but only partially inhibited by ATR (Harries, Parkes, Lessof & Orr, 1981). This suggests that various agents which produce bronchoconstriction or bronchial hyperreactivity which is blocked by DSCG may act through a reflex arc involving baroreceptors. This hypothesis is supported by work done with acetylsalicylic acid (ASA) and tartrazine. Both drugs have been reported to produce constriction in the large airways of anesthetized, paralyzed guinea-pigs (Peterson, Biggs & Aaron, 1980; Biggs, Peterson & Aaron, 1981) and to enhance bronchoconstriction induced by histamine (Biggs & Peterson, 1979; Biggs, Peterson & Aaron, 1981). Like responses to diazoxide, the constriction produced by these drugs was unaffected by ATR or vagotomy, but was abolished by glossopharyngealotomy, DSCG or MEP (Biggs, Peterson & Aaron, 1981; Peterson, Biggs & Aaron, 1981). Others have reported that DSCG prevented or abolished bronchoconstriction induced by ASA or indomethacin in humans (Basomba, Romar, Pelaez, Villalmanzo & Campos, 1976; Martelli & Usandivàras, 1977; Martelli, 1979).

Finally, as alpha$_2$-receptors were implicated in the responses to both 5HT and diazoxide, this work might provide a more rational basis for the selection and use of alpha-blocking agents in the treatment of asthma.

Table 1. Results of Stimulation Experiments

| NERVE OR GANGLION STIMULATED | RESULT | REFERENCE |
|---|---|---|
| Vagus | C | 1 |
| Vagus | ↓RESP | 5 |
| Vagus | C & R | 7 |
| Vagus | C & R | 9 |
| Cervical vagus or sympathetic | C | 8 |
| Cervical vagus or sympathetic | C & R | 4 |
| Cervical sympathetic | 0,C or R | 2 |
| Vagosympathetic | C & R | 3 |
| Vagus or stellate | C & R | 6 |
| Stellate | 0 or R | 1 |
| Stellate | C & R | 2 |
| Carotid sinus | ↑RESP | 5 |

Result code: C = constriction, R = relaxation, 0 = no effect, RESP = respiration

References: (1) Cabezas *et al.*, 1971; (2) Daly, Elsden, Hebb, von Ludany & Petrovskaia, 1942; (3) Dixon & Brodie, 1903; (4) Dixon & Ranson, 1912; (5) Douglas, Innes & Kosterlitz, 1950; (6) Hammarstrom & Sjostrand, 1979; (7) Head, 1889; (8) Hebb, 1940; (9) Roy & Brown, 1885.

TABLE 2. EFFECTS OF VARIOUS DRUGS AND TREATMENTS ON $R_L$ AND $C_L$

Changes in baseline values of $R_L$ and $C_L$ were measured within 3 min of drug administration or nerve section; all measurements returned to control values in 5-15 min.

| TREATMENT | % INCREASE $R_L$ Mean (SEM)* | % DECREASE $C_L$ Mean (SEM)* | n |
|---|---|---|---|
| Saline 0.5 ml | 0 (0) | 0.2 (0) | 15 |
| 1 ml | 0 (0) | 1.2 (0.9) | 36 |
| DRUGS (mg/kg) | | | |
| ATR (0.05) | 0 (0) | 2.2 (2.7) | 6 |
| AMI (0.05) | 0 (0) | 6.3 (4.2) | 6 |
| AZP (0.5) | 0 (0) | 0 (0) | 4 |
| (1) | 0 (0) | 4.7 (3.2) | 7 |
| BRE (7.5) | 0 (0) | 0.9 (0.9) | 4 |
| (15) | 0 (0) | 1 (3.5) | 4 |
| CLD (0.15) | 23.6 (3) | 0.9 (0.9) | 4 |
| DEX (5) | 5.9 (3) | 2.3 (1.5) | 7 |
| DSCG (10) | 0 (0) | 0 (0) | 4 |
| 6HD (5) | 1.8 (1.8) | - | 4 |
| MEP (0.1) | 0.7 (0.7) | 9.3 (3.8) | 5 |
| M (0.5) | 2.2 (2.2) | 3.4 (3.4) | 4 |
| (1) | 1.8 (1.8) | 1 (5.6) | 4 |

Table 2 Continued

| TREATMENT | % INCREASE $R_L$ Mean (SEM)* | % DECREASE $C_L$ Mean (SEM)* | n |
|---|---|---|---|
| PHE (0.05) | 9.6 (6.8) | 3.8 (3.8) | 5 |
| PRO (1) | 2.7 (2.7) | 0.4 (1.5) | 5 |
| TRI (0.5) | 0.9 (0.9) | 2 (1.3) | 6 |
| (1) | 0 (0) | 0.8 (0.8) | 6 |
| NERVE SECTION | | | |
| BILATERAL | | | |
| Glossopharyngealotomy | 2.6 (2.5) | 16.9(5) | 11 |
| Vagotomy: | | | |
| mid-cervical | 0 (0) | 0.3 (2.6) | 4 |
| high | 0.4 (8.1) | 2.4 (7.5) | 4 |
| UNILATERAL | | | |
| Vagotomy | 0 (0) | 1.3 (1.3) | 3 |
| Glossopharyngealotomy | 0 (0) | 10.7(5.4) | 5 |

*) SEM = Standard error of the mean

Table 3. Baseline Values of $R_L$ and $C_L$.

| TREATMENT | $R_L$ (ml/sec/cm $H_2O$) Mean (SEM) | $C_L$ (ml/cm $H_2O$ Mean (SEM) | n |
|---|---|---|---|
| Normal, controls | 0.37 (0.02) | 0.42 (0.02) | 5 |
| 6HD[a], 35 mg/kg | 0.41 (0.01) | 0.41 (0.01) | 6 |
| RES[a], 2.5 mg/kg | 0.35 (0.02) | 0.41 (0.02) | 7 |
| Decentralization | 0.35 (0.01) | 0.33 (0.01) | 5 |

a) Drugs were given intraperitoneally, 24 hours before testing.

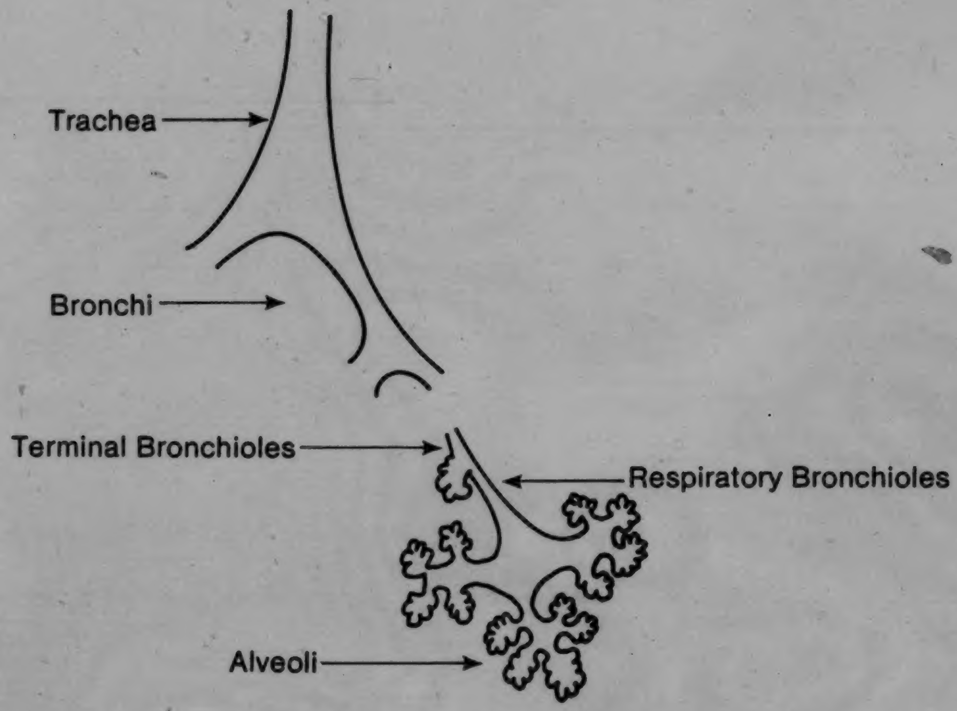
Trachea
Bronchi
Terminal Bronchioles
Respiratory Bronchioles
Alveoli

Figure 1. The major subdivisions of the airways.

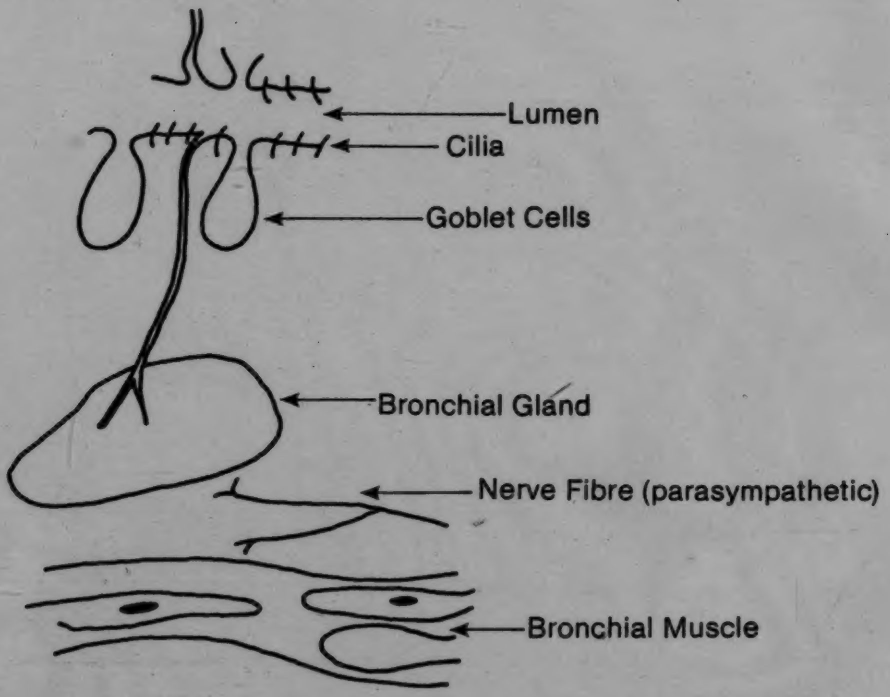
Lumen
Cilia
Goblet Cells
Bronchial Gland
Nerve Fibre (parasympathetic)
Bronchial Muscle

Figure 2. Some structural components of the airways.

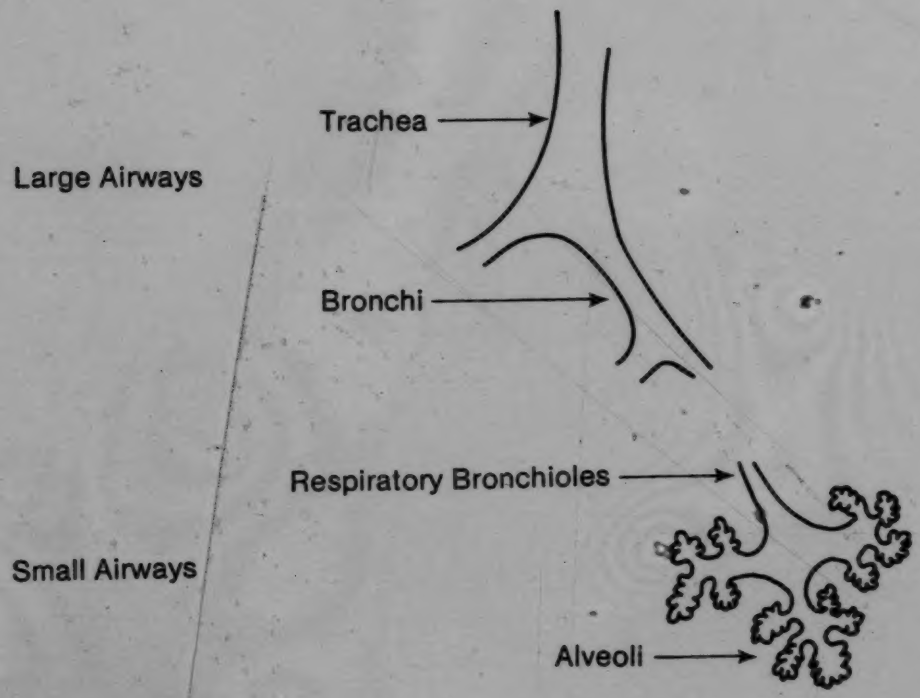
Trachea
Large Airways
Bronchi
Respiratory Bronchioles
Small Airways
Alveoli

Figure 3. The large and small airways.

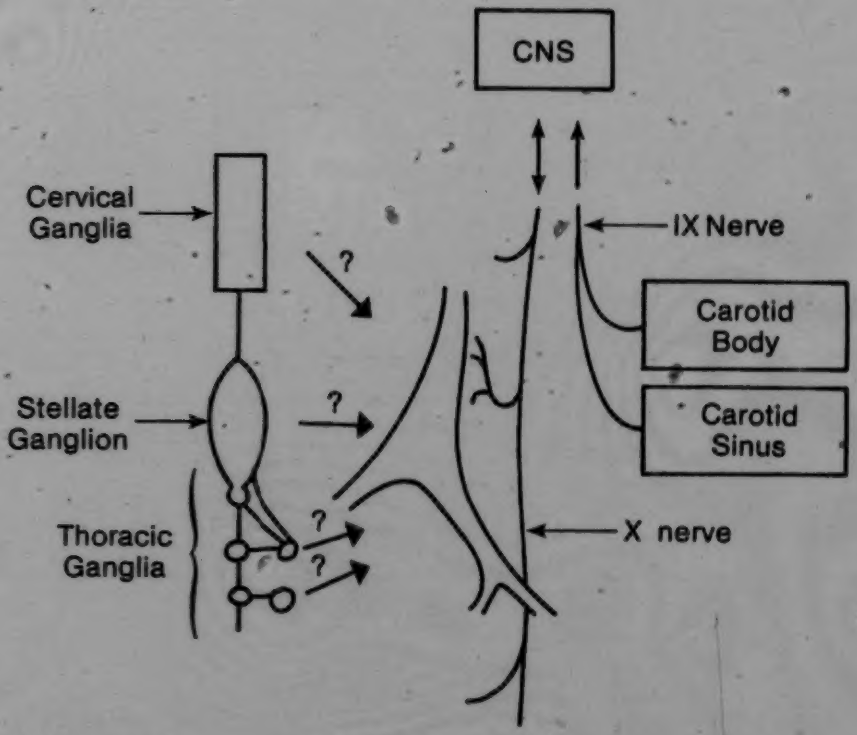
CNS
Cervical Ganglia
Stellate Ganglion
Thoracic Ganglia
?
?
?
?
IX Nerve
Carotid Body
Carotid Sinus
X nerve

Figure 4. Nervous pathways associated with reflex bronchoconstriction.

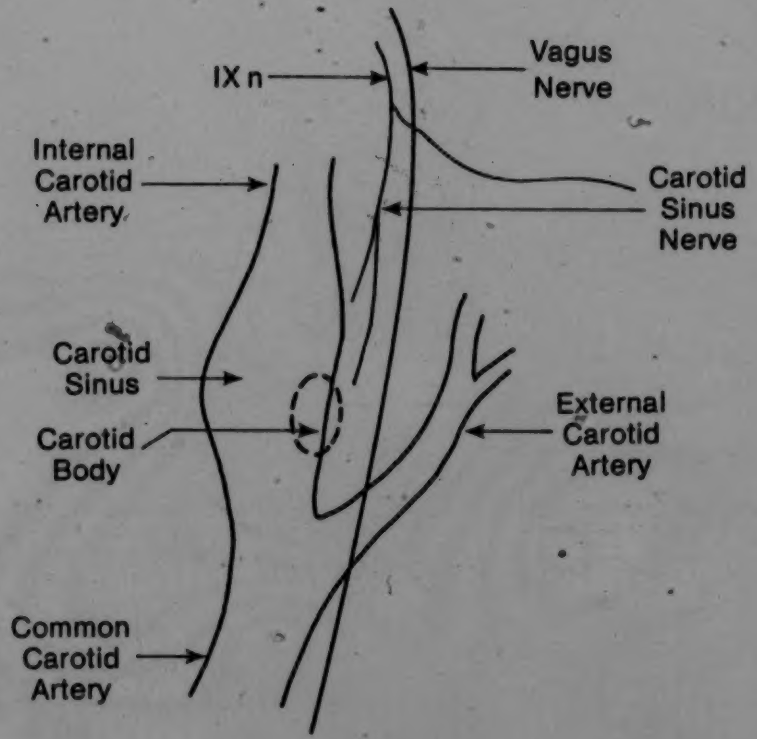
IX n
Vagus Nerve
Internal Carotid Artery
Carotid Sinus Nerve
Carotid Sinus
Carotid Body
External Carotid Artery
Common Carotid Artery

Figure 5. The general location of the carotid sinus and carotid body.

Note: The actual location of these structures is species-dependent.

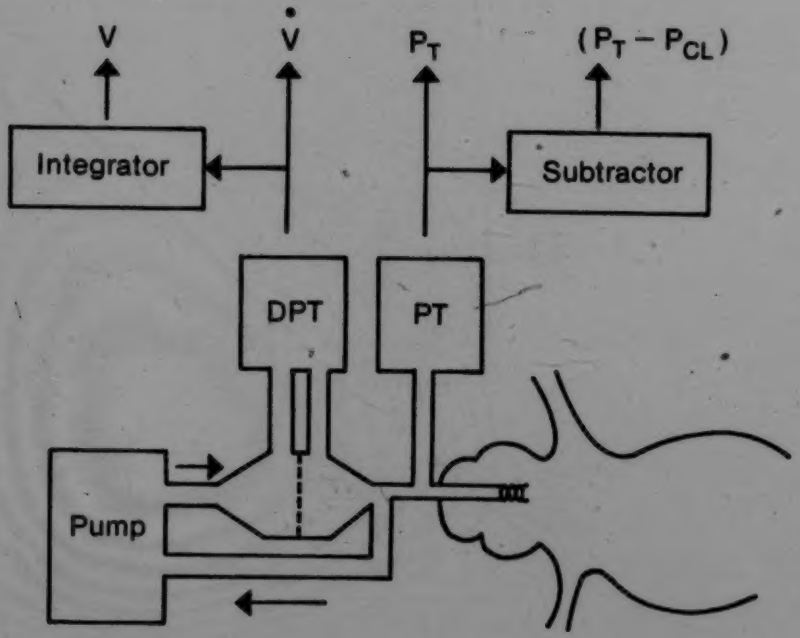
V
$\dot{V}$
$P_T$
$(P_T - P_{CL})$
Integrator
Subtractor
DPT
PT
Pump

Figure 6.. Apparatus for measurements of $C_L$ and $R_L$.

$V$ = Volume

$\dot{V}$ = Flow rate

DPT = Differential pressure transducer

PT = Pressure transducer

$P_{CL}$ = Compliance component of pressure

$P_T$ = Tracheal pressure

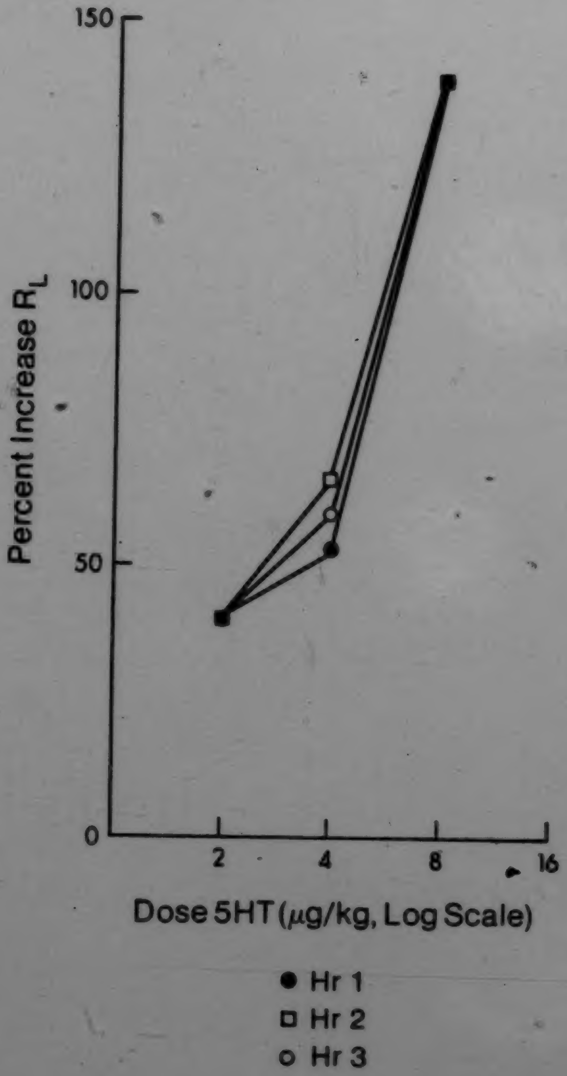

Figure 7. Effects of 5HT on $R_L$.

Responses, measured at 1 hr intervals, were dose-related and reproducible for periods of three hr.

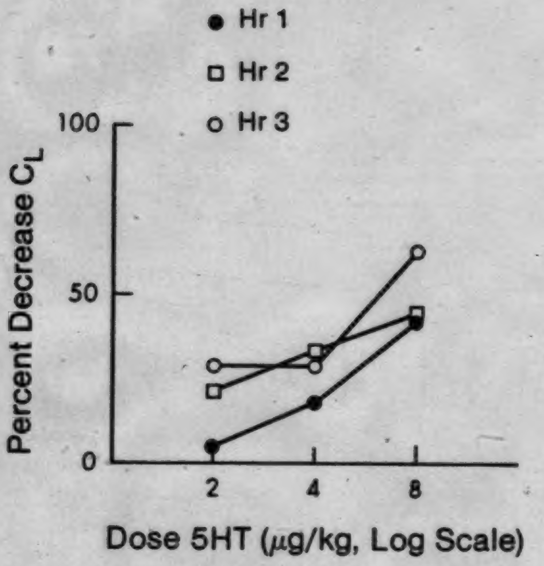

Figure 8. Effects of 5HT on $C_L$.

Responses, measured at 1 hr intervals, were dose-related but not reproducible.

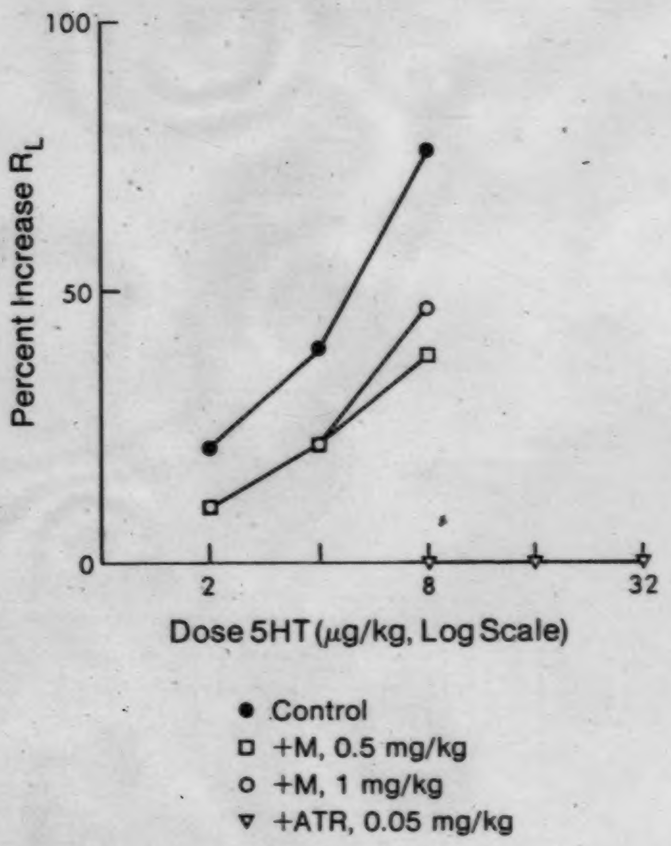

Figure 9. Effects of methysergide (M), followed by atropine (ATR), on 5HT-induced increases in $R_L$.

M, 0.5 mg/kg, reduced responses to 5HT. Increasing the dose of M did not produce further inhibition, but the combination of M and ATR, 0.05 mg/kg, eliminated responses to 5HT.

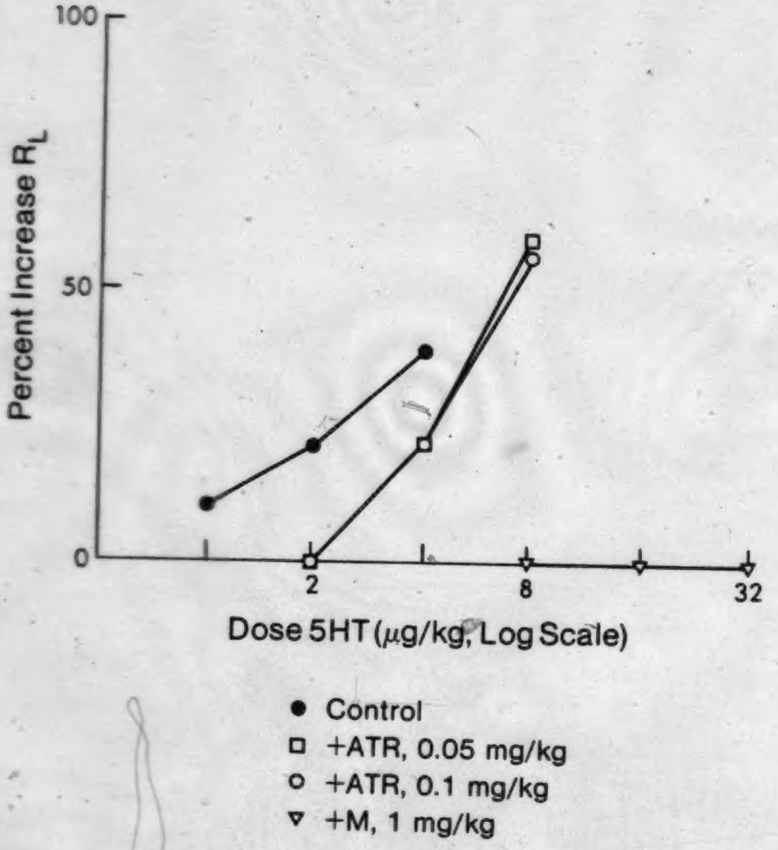

Figure 10. Effect of atropine (ATR), followed by methysergide (M), on 5HT-induced increases in $R_L$.

ATR, 0.05 mg/kg, reduced responses to 5HT. Increasing the dose of ATR did not produce further inhibition, but the combination of ATR and M, 1 mg/kg, eliminated responses to 5HT.

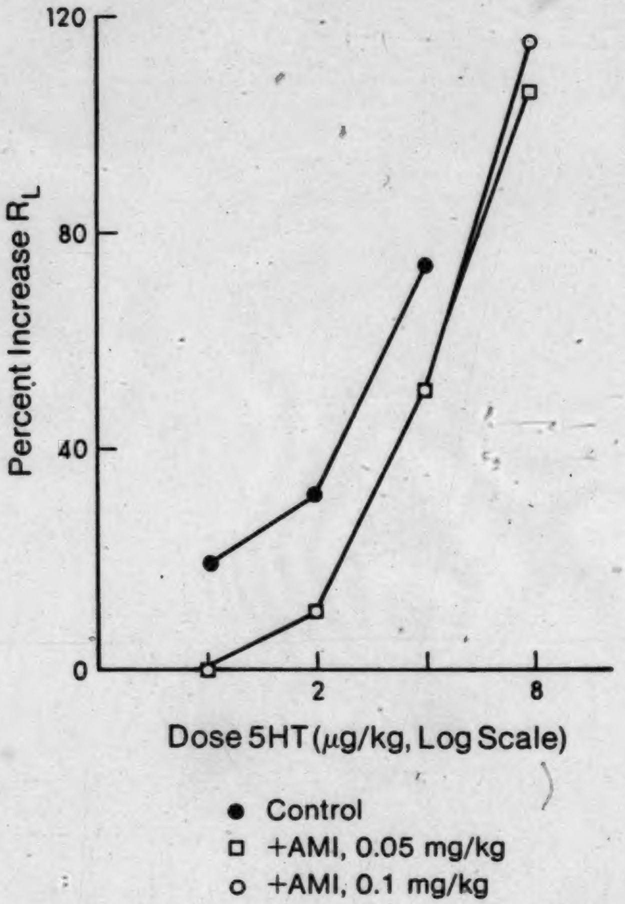

Figure 11. Effects of atropine methiodide (AMI) on 5HT-induced increases in $R_L$.

AMI, 0.05 mg/kg, reduced responses to 5HT. Increasing the dose of AMI did not produce further inhibition of the responses to 5HT.

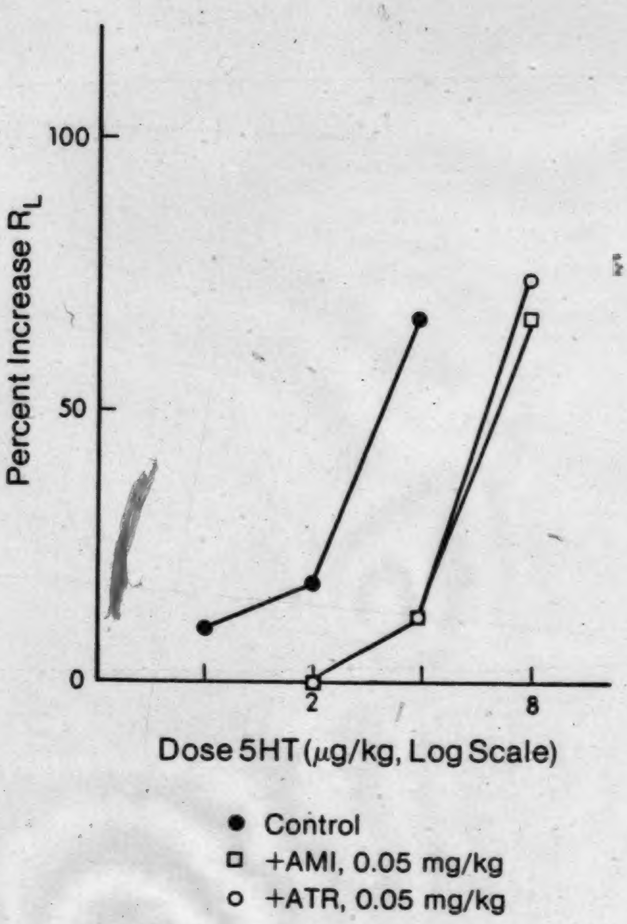

Figure 12. Effects of atropine methiodide (AMI), followed by atropine (ATR), on 5HT-induced increases in $R_L$.

AMI, 0.05 mg/kg, reduced responses to 5HT. ATR, 0.05 mg/kg, given after AMI produced no additional inhibition of the responses to 5HT.

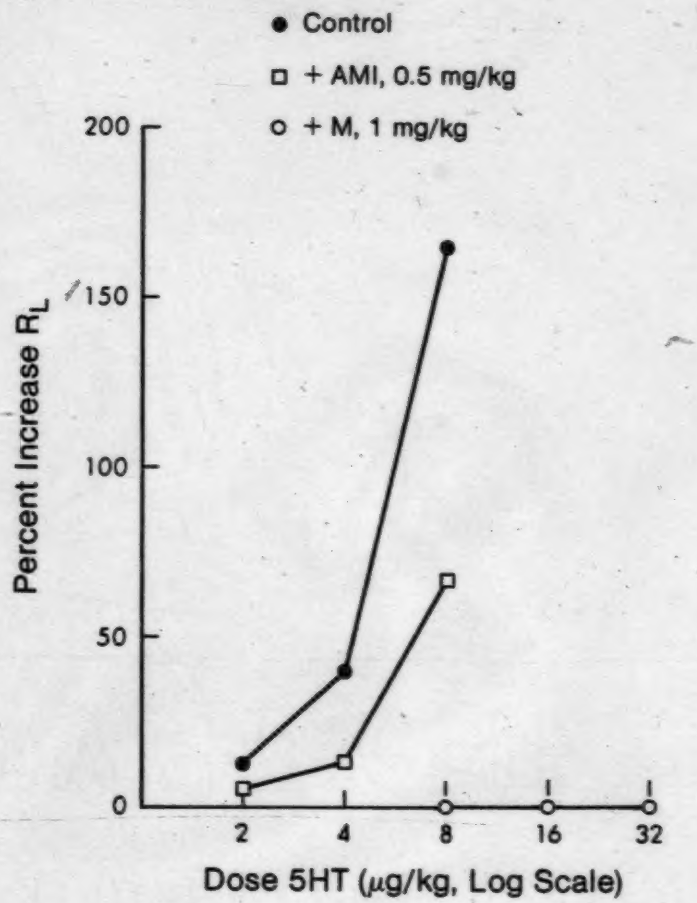

Figure 13. Effects of atropine methiodide (AMI), followed by methysergide (M), on 5HT-induced increases in $R_L$.

AMI, 0.05 mg/kg, reduced the responses to 5HT. The combination of AMI and M, 1 mg/kg, eliminated responses to 5HT.

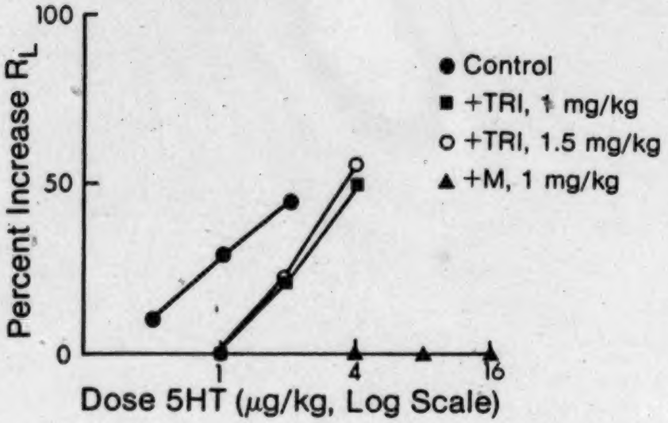

Figure 14. Effects of trimethaphan (TRI), followed by methysergide (M), on 5HT-induced increases in $R_L$.

TRI, 1 mg/kg, reduced responses to 5HT. Increasing the dose of TRI did not produce further inhibition, but the combination of TRI and M, 1 mg/kg, eliminated the responses to 5HT.

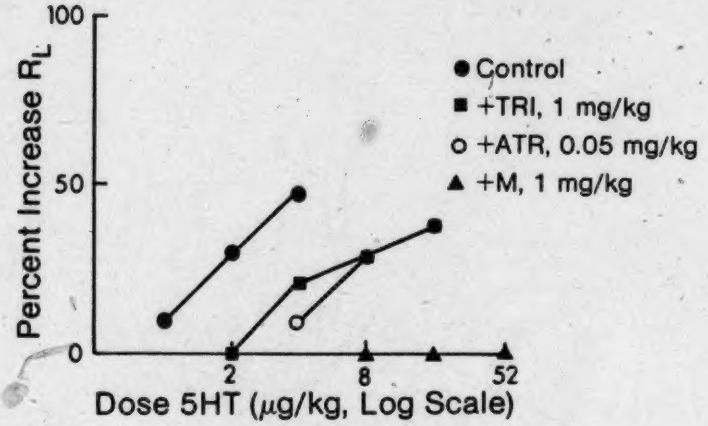

Figure 15. Effects of trimethaphan (TRI), followed by atropine (ATR) and then methysergide (M), on 5HT-induced increases in $R_L$.

TRI, 1 mg/kg, reduced responses to 5HT. After animals were given TRI, ATR, 0.05 mg/kg, no longer inhibited responses to 5HT, whereas addition of M, 1 mg/kg, abolished responses to 5HT.

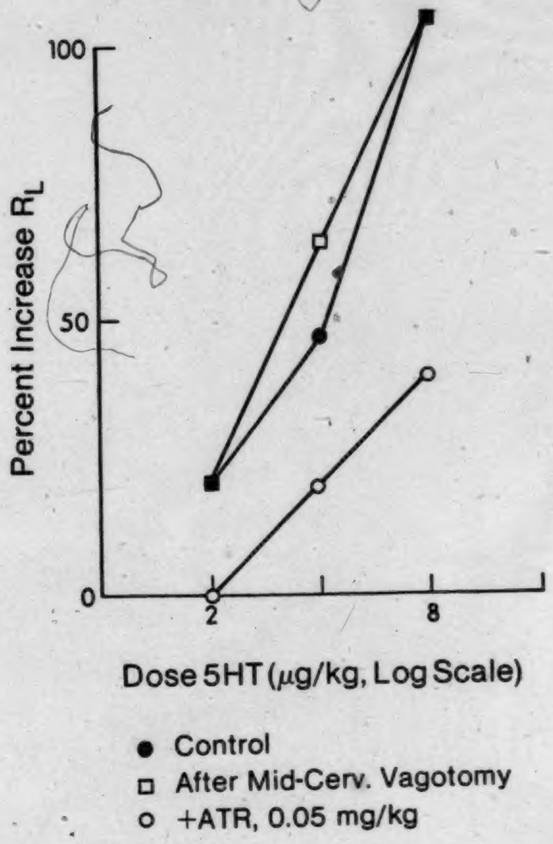

Figure 16. Effects of bilateral, mid-cervical vagotomy, followed by atropine (ATR), on 5HT-induced increases in $R_L$.

Vagotomy did not significantly affect responses to 5HT. After vagotomy, ATR, 0.05 mg/kg, still reduced responses to 5HT.

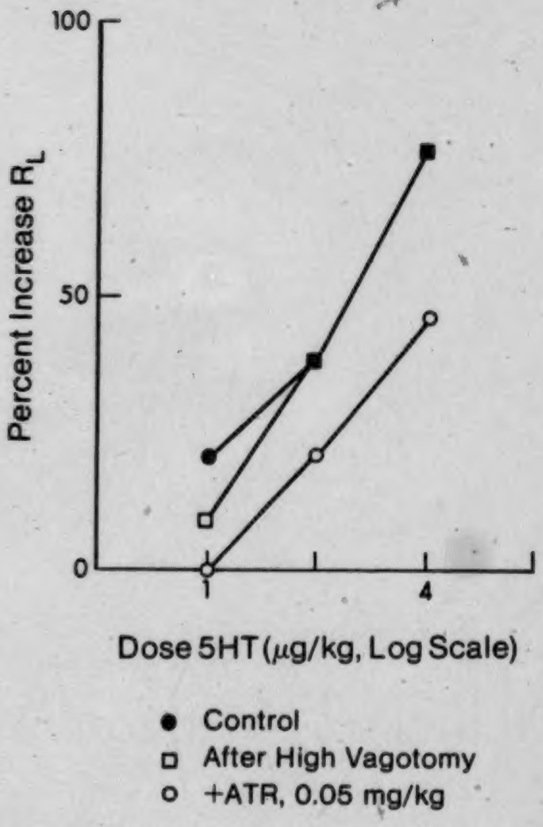

Figure 17. Effects of bilateral, high vagotomy, followed by atropine (ATR), on 5HT-induced increases in $R_L$.

Vagotomy did not significantly affect responses to 5HT. After vagotomy, ATR, 0.05 mg/kg, reduced responses to 5HT.

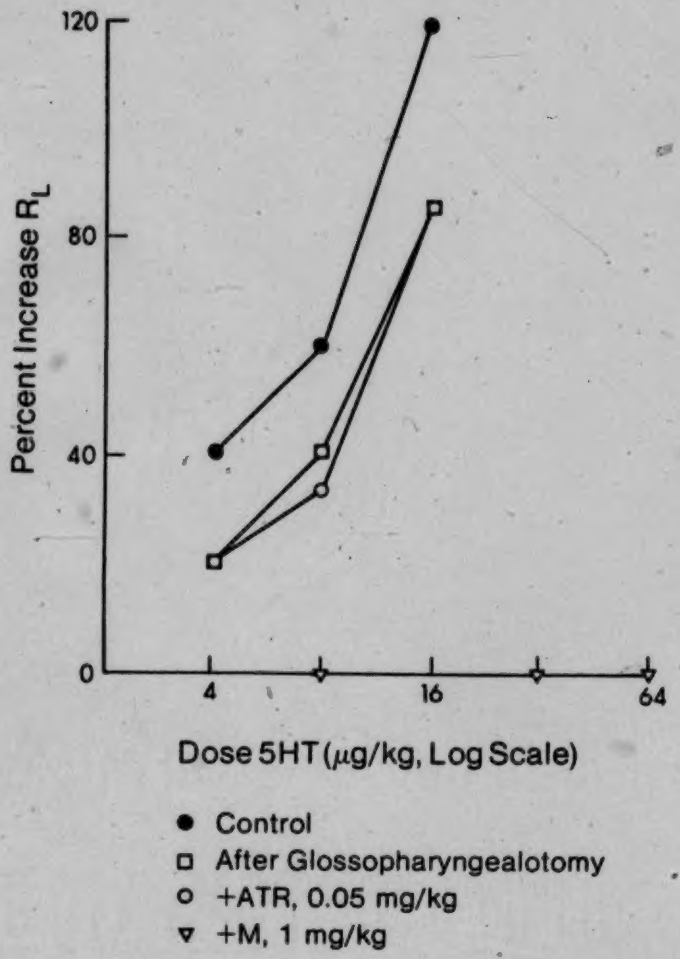

Figure 18. Effects of bilateral glossopharyngealotomy, followed by atropine (ATR) and then methysergide (M), on 5HT-induced increases in $R_L$.

Glossopharyngealotomy reduced responses to 5HT. After glossopharyngealotomy, ATR, 0.05 mg/kg, produced no significant effects on the responses to 5HT, whereas M, 1 mg/kg, abolished the responses.

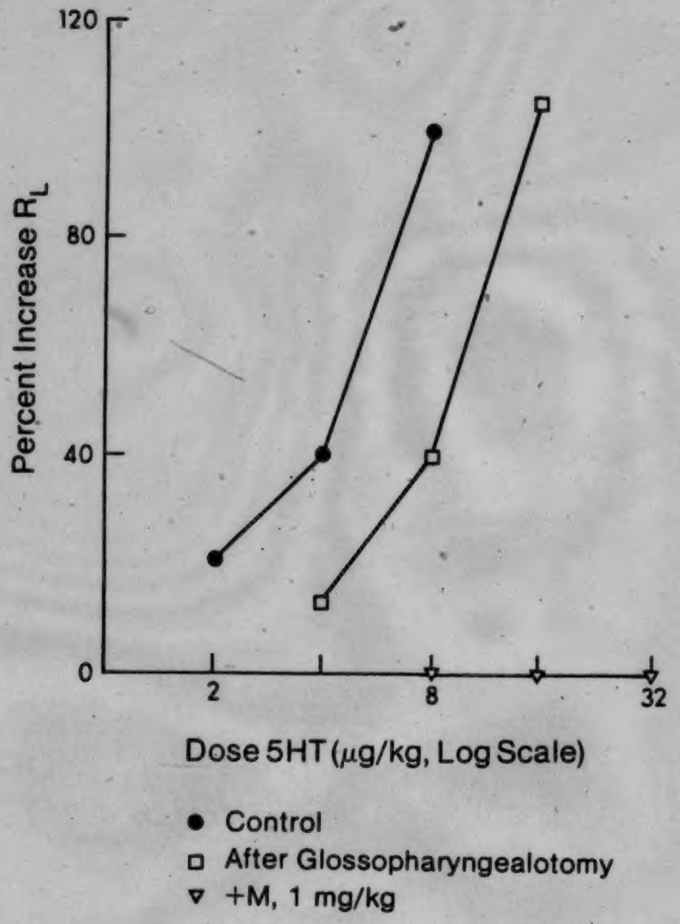

Figure 19. Effects of bilateral glossopharyngealotomy, followed by methysergide (M), on 5HT-induced increases in $R_L$.

Glossopharyngealotomy reduced responses to 5HT. After nerve section, M, 1 mg/kg, eliminated the responses to 5HT.

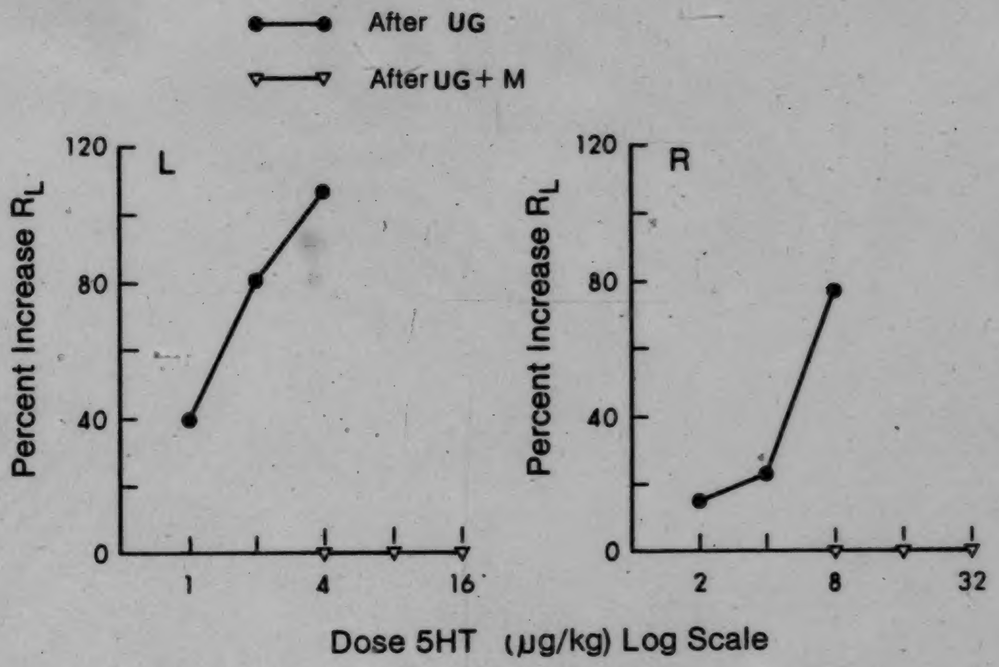

Figure 20. Effects of methysergide (M) on 5HT-induced increases in $R_L$ obtained in animals after either left (L) or right (R) unilateral glossopharyngealotomy (UG) had been performed.

M, 1 mg/kg, eliminated responses to 5HT after the left or right glossopharyngeal nerve was sectioned.

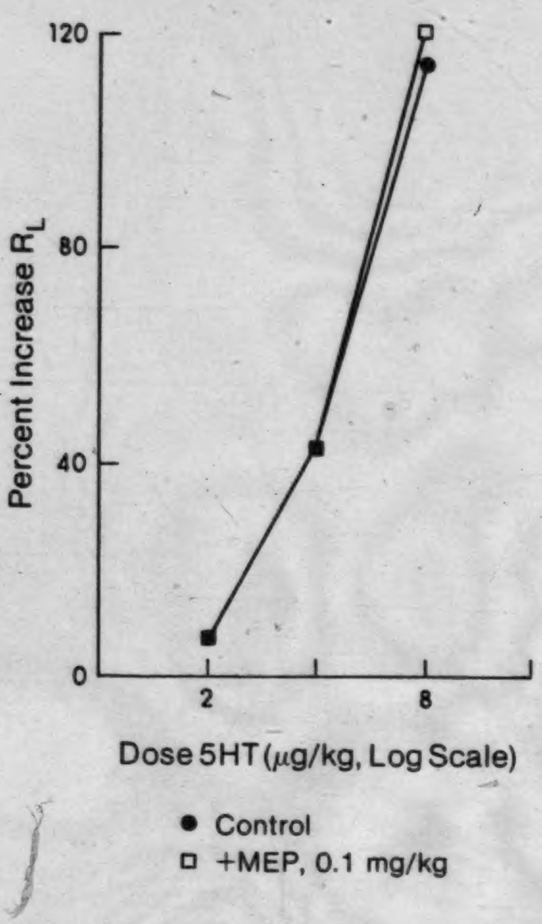

Figure 21. Effects of mepyramine (MEP) on 5HT-induced increases in $R_L$.

MEP, 0.1 mg/kg, produced no significant effects on the responses to 5HT.

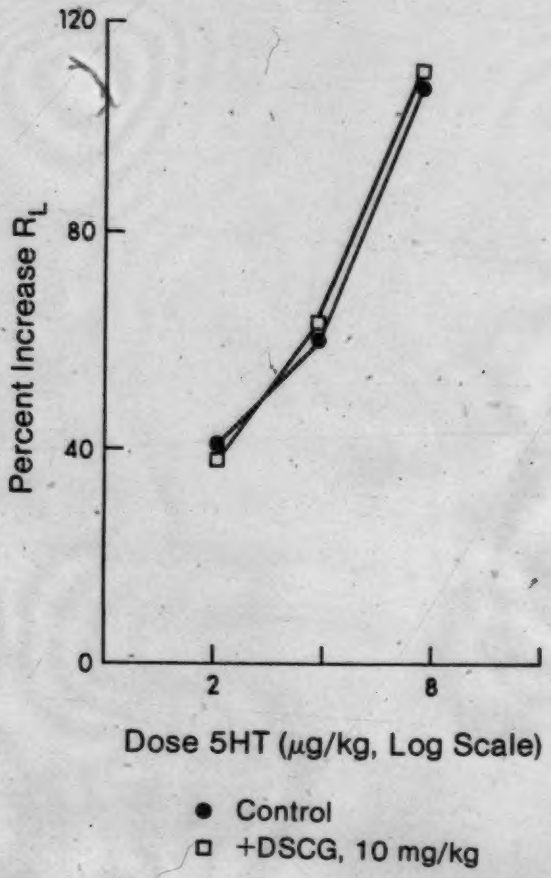

Figure 22. Effects of disodium cromoglycate (DSCG) on 5HT-induced increases in $R_L$.

DSCG, 10 mg/kg, produced no significant effects on the responses to 5HT.

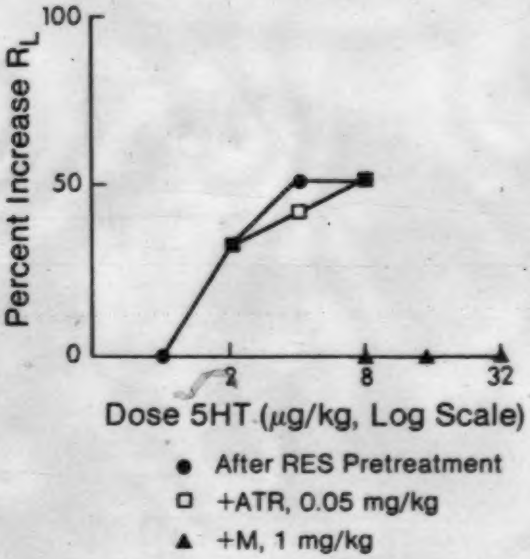

Figure 23. Effects of atropine (ATR), followed by methysergide (M), on 5HT-induced increases in $R_L$ observed in animals pretreated with reserpine (RES), 2.5 mg/kg.

ATR, 0.05 mg/kg, produced no significant effects on the responses to 5HT in reserpinized animals, whereas the addition of M, 1 mg/kg, abolished the responses to 5HT in these animals.

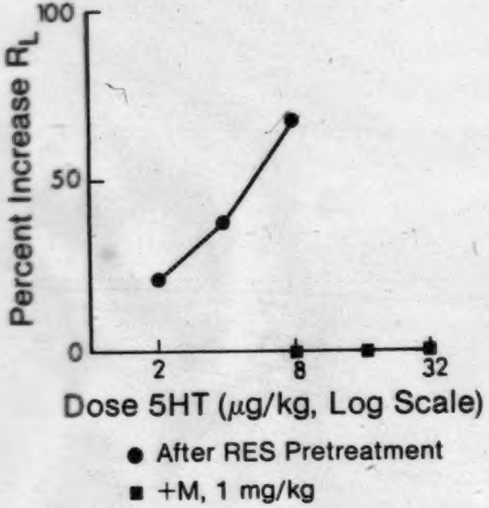

Figure 24. Effects of methysergide (M) on 5HT-induced increases in $R_L$ obtained in animals pretreated with reserpine (RES), 2.5 mg/kg.

M, 1 mg/kg, abolished responses to 5HT in reserpinized animals.

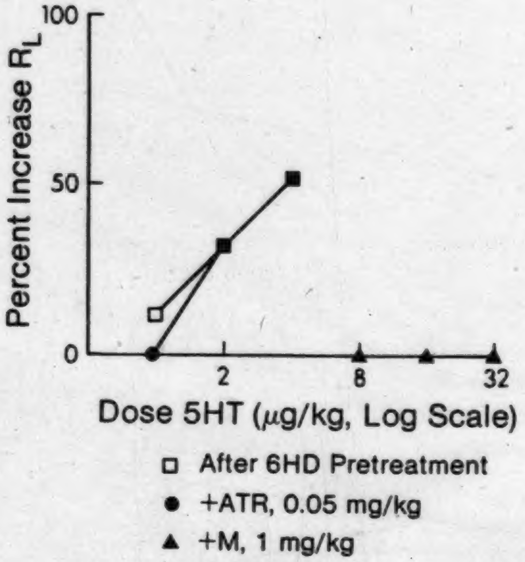

Figure 25. Effects of atropine (ATR), followed by methysergide (M), on 5HT-induced increases in $R_L$ obtained in animals pretreated with 6-hydroxydopamine (6HD), 35 mg/kg.

ATR, 0.05 mg/kg, produced no significant effects on responses to 5HT in animals pretreated with 6HD, whereas the addition of M, 1 mg/kg, completely abolished the responses to 5HT in these animals.

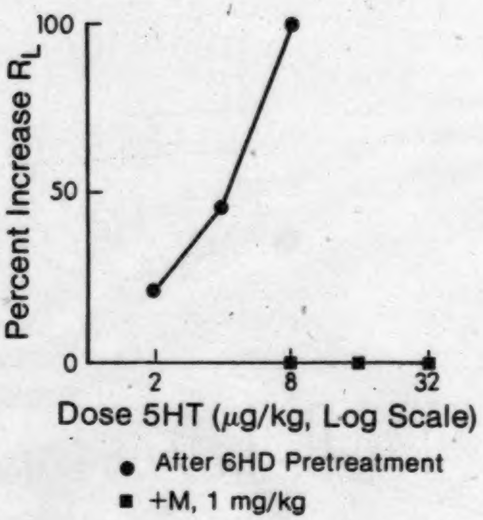

Figure 26. Effects of methysergide (M) on 5HT-induced increases in $R_L$ obtained in animals pretreated with 6-hydroxydopamine (6HD), 35 mg/kg.

M, 1 mg/kg, abolished the responses to 5HT in animals pretreated with 6HD.

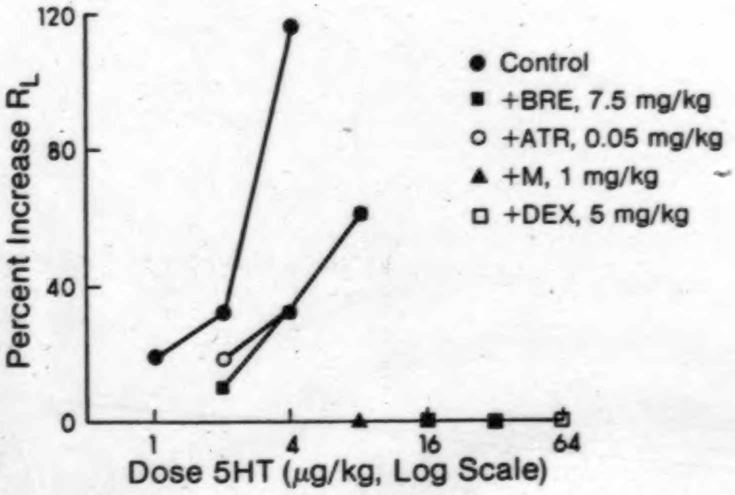

Figure 27. Effects of bretylium (BRE), followed by atropine (ATR), methysergide (M) and then dexamphetamine (DEX), on 5HT-induced increases in $R_L$.

ATR, 0.05 mg/kg, produced no significant effects on responses to 5HT in animals treated with BRE, 7.5 mg/kg, whereas M, 1 mg/kg, abolished the responses to 5HT in these animals. DEX, 5 mg/kg, was unable to reverse blockade in animals that had received ATR.

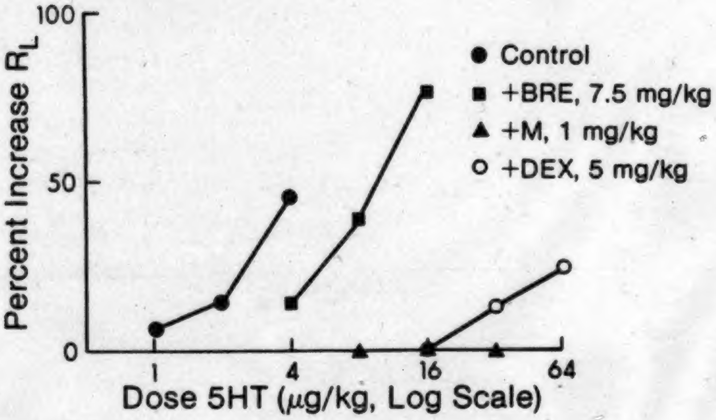

Figure 28. Effects of bretylium (BRE), followed by methysergide (M) and then dexamphetamine (DEX), on 5HT-induced increases in $R_L$.

M, 1 mg/kg, abolished responses to 5HT in animals treated with BRE, 7.5 mg/kg. The blockade was partially reversed with DEX, 5 mg/kg.

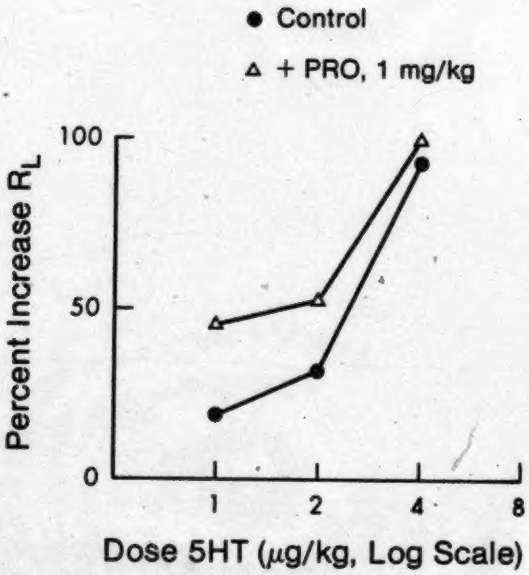

Figure 29. Effects of propranolol (PRO) on 5HT-induced increases in $R_L$.

PRO, 1 mg/kg, enhanced responses to 5HT.

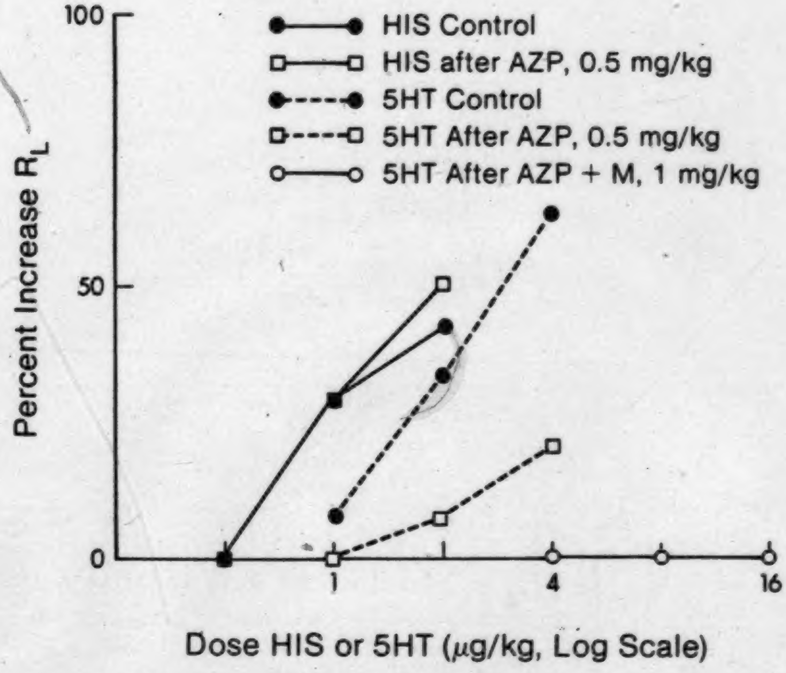

Figure 30. Effects of azapetine (AZP, 0.5 mg/kg) on histamine (HIS)-induced increases in $R_L$ and effects of AZP (0.5 mg/kg), followed by methysergide (M), on 5HT-induced increases in $R_L$.

AZP, 0.5 mg/kg, reduced responses to 5HT but produced no significant effects on responses to HIS. The combination of AZP, 0.5 mg/kg, and M, 1 mg/kg, abolished responses to 5HT.

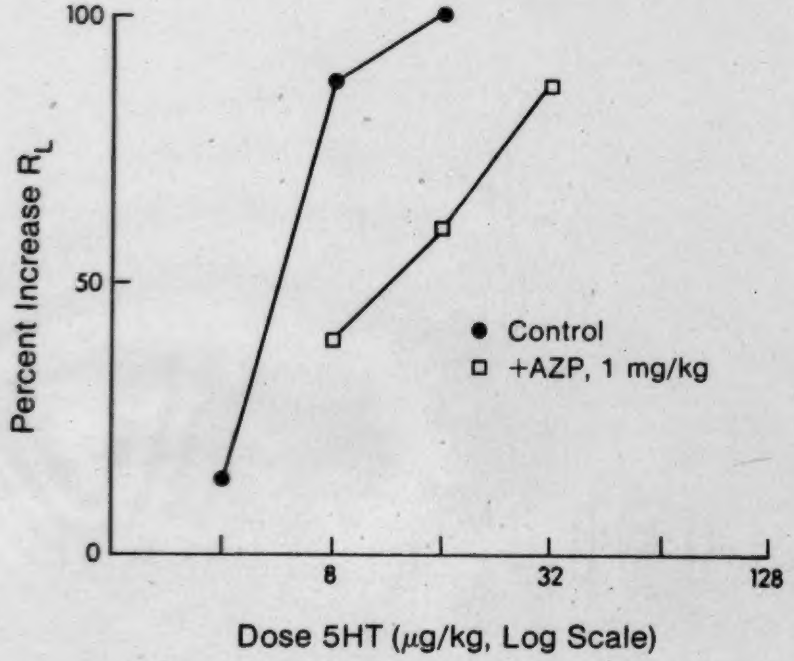

Figure 31. Effects of azapetine (AZP), 1 mg/kg, on 5HT-induced increases in $R_L$.

AZP, 1 mg/kg, reduced responses to 5HT.

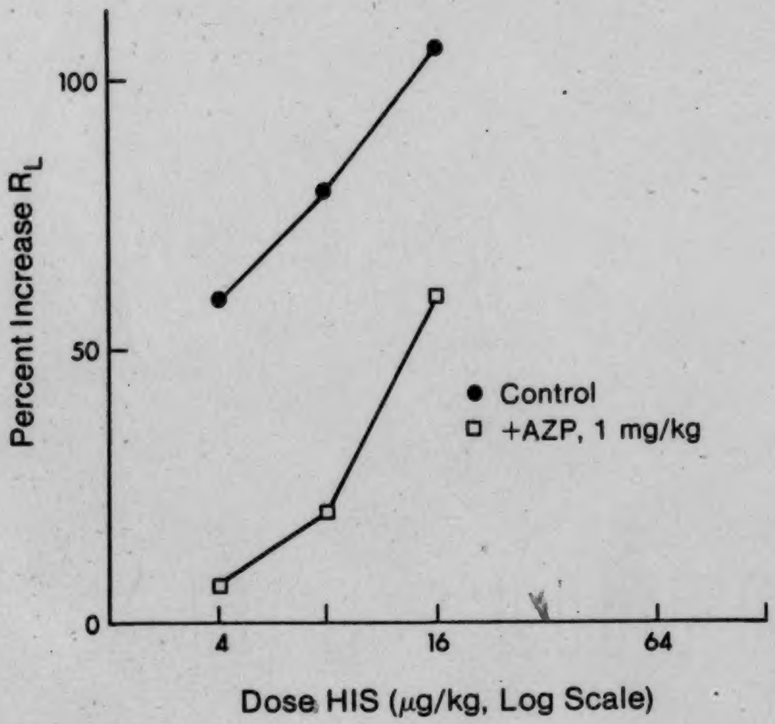

Figure 32. Effects of azapetine (AZP), 1 mg/kg, on histamine (HIS)-induced increases in $R_L$.

AZP, 1 mg/kg, reduced responses to HIS.

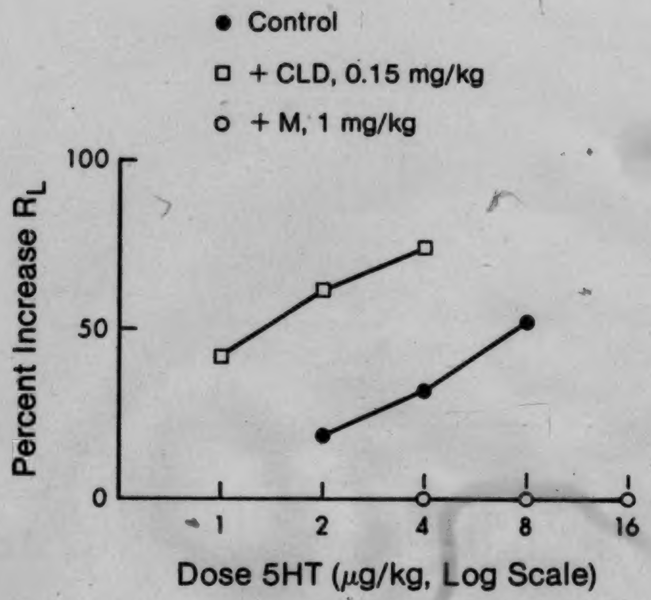

Figure 33. Effects of clonidine (CLD), followed by methysergide (M), on 5HT-induced increases in $R_L$.

CLD, 0.15 mg/kg, enhanced the responses to 5HT. The combination of CLD and M, 1 mg/kg, abolished responses to 5HT.

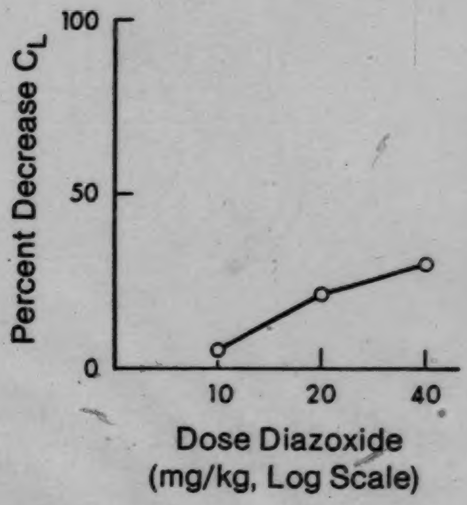

Figure 34. Effects of diazoxide on $C_L$.

Diazoxide produced dose-related decreases in $C_L$.

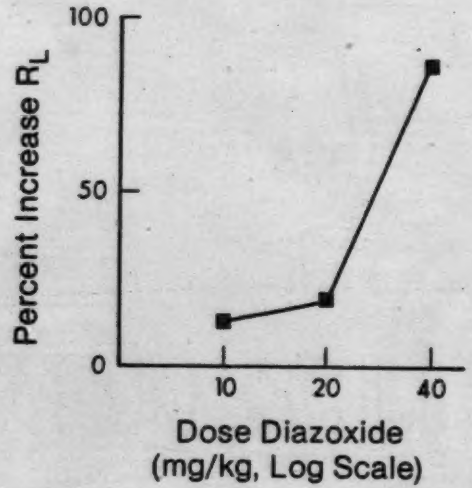

Figure 35. Effects of diazoxide on $R_L$.

Diazoxide produced dose-related increases in $R_L$.

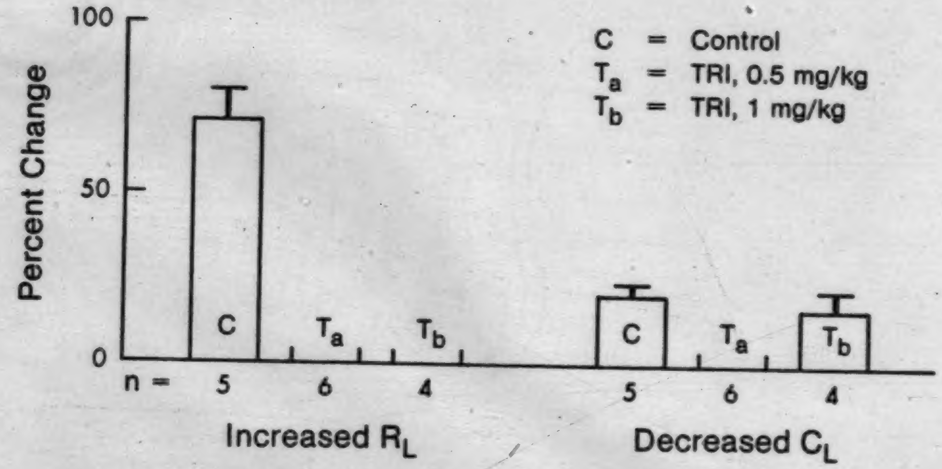

Figure 36. Effects of trimethaphan (TRI) on responses to diazoxide, 40 mg/kg.

TRI, 0.5 and 1 mg/kg, consistently abolished diazoxide-induced increases in $R_L$, but produced inconsistent effects on diazoxide-induced decreases in $C_L$. Bars show mean responses and vertical lines indicate one S.E.M.

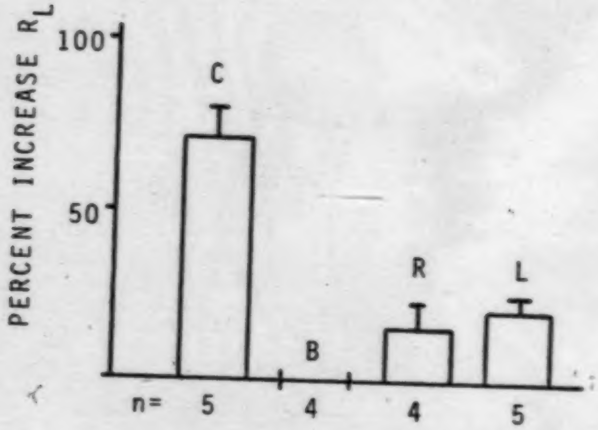

Figure 37. Effects of bilateral (B) and left (L) or right (R) unilateral glossopharyngealotomy on increases in $R_L$ produced by diazoxide, 40 mg/kg.

C shows responses obtained in control animals. Unilateral glossopharyngealotomy reduced responses to diazoxide, whereas bilateral glossopharyngealotomy abolished responses to diazoxide. Bars show mean responses and vertical lines indicate one S.E.M.

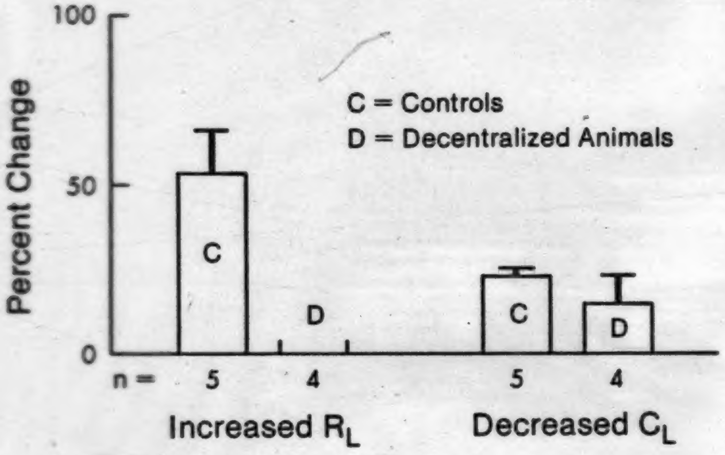

Figure 38. Effects of decentralization on responses to diazoxide, 20 mg/kg.

Decentralization abolished diazoxide-induced increases in $R_L$, but produced no significant effects on diazoxide-induced decreases in $C_L$. Bars show mean responses and vertical lines indicate one S.E.M.

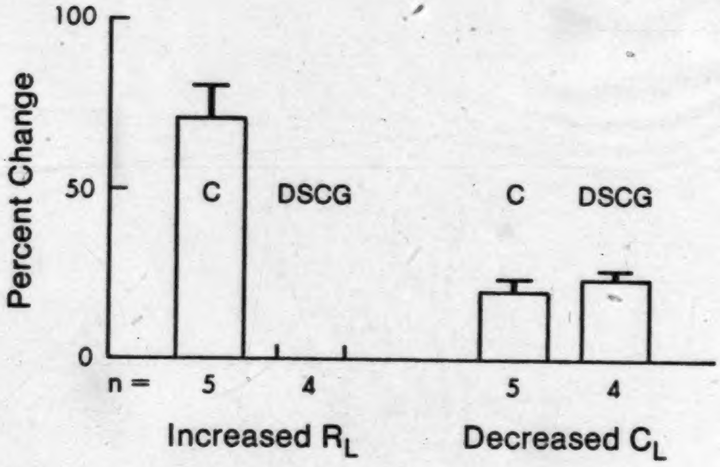

Figure 39. Effects of disodium cromoglycate (DSCG) on control responses (C) to diazoxide, 40 mg/kg.

DSCG, 10 mg/kg, abolished diazoxide-induced increases in $R_L$, but produced no significant effects on diazoxide-induced decreases in $C_L$. Bars show mean responses and vertical lines indicate one S.E.M.

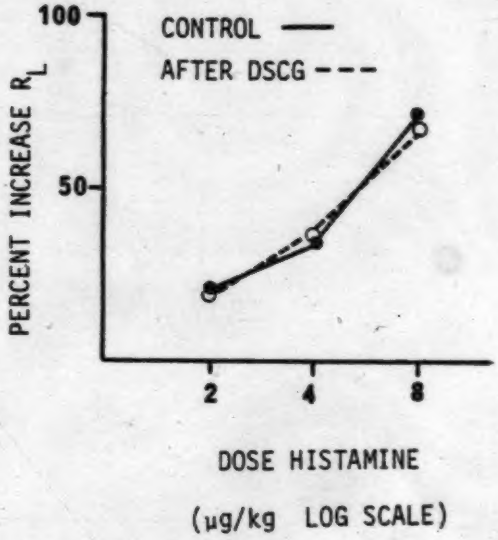

Figure 40. Effects of disodium cromoglycate (DSCG, 10 mg/kg) on histamine-induced increases in $R_L$.

DSCG, 10 mg/kg, produced no significant effects on histamine-induced increases in $R_L$.

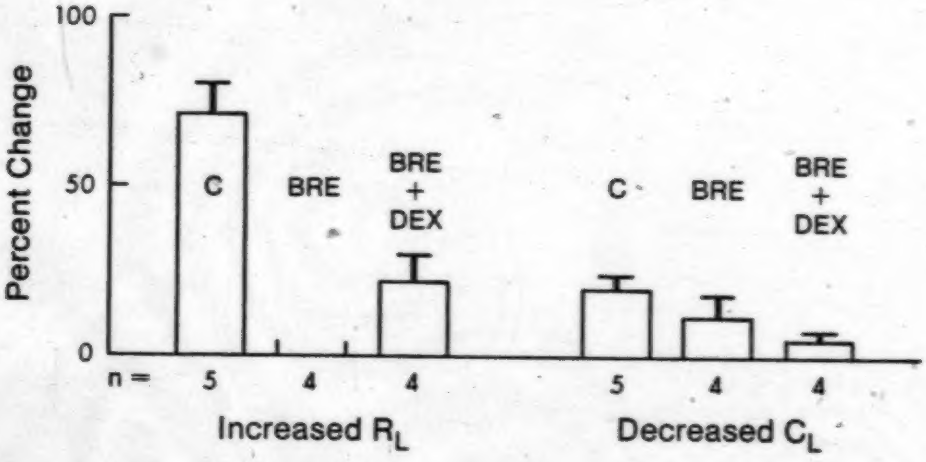

Figure 41. Effects of bretylium (BRE), and BRE followed by dexamphetamine (DEX), on control responses (C) to diazoxide, 40 mg/kg.

BRE, 7.5 mg/kg, abolished diazoxide-induced increases in $R_L$ without significantly affecting diazoxide-induced decreases in $C_L$. Partial recovery of the diazoxide-induced increases in $R_L$ was observed after both BRE and DEX had been administered. Diazoxide-induced decreases in $C_L$ were reduced after the combination of BRE and DEX were given. Bars show mean responses and lines indicate one S.E.M.

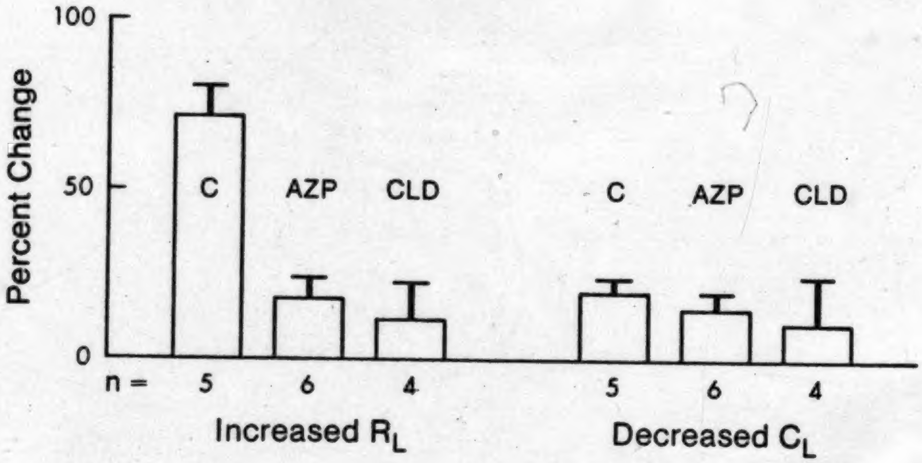

Figure 42. Effects of azapetine (AZP) and clonidine (CLD) on control responses (C) to diazoxide, 40 mg/kg.

Both AZP, 0.5 mg/kg, and CLD, 0.15 mg/kg, reduced diazoxide-induced increases in $R_L$ without significantly affecting diazoxide-induced decreases in $C_L$. Bars show mean responses and vertical lines indicate one S.E.M.

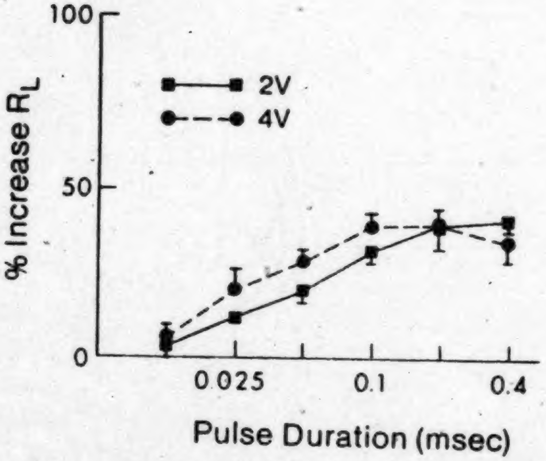

Figure 43. Changes in $R_L$ produced by nerve stimulation at 2 or 4 V.

Nerve stimulation at 2 or 4 V produced increases in $R_L$ which were dependent on the pulse duration. Points show the mean responses obtained in 12 animals and the vertical lines indicate one S.E.M.

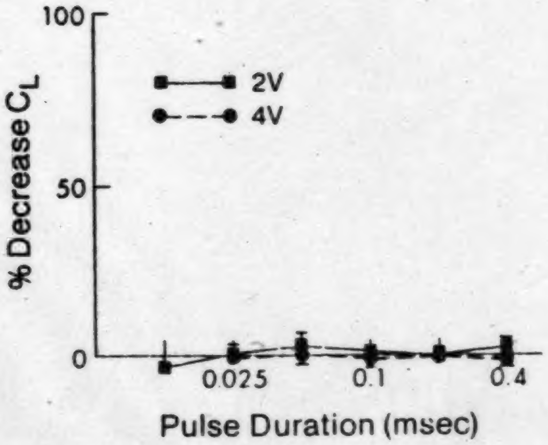

Figure 44. Changes in $C_L$ produced by nerve stimulation at 2 or 4 V.

No significant changes in $C_L$ were noted after nerve stimulation at either 2 or 4 V. Points show mean responses obtained in 7 animals and the vertical lines indicate one S.E.M.

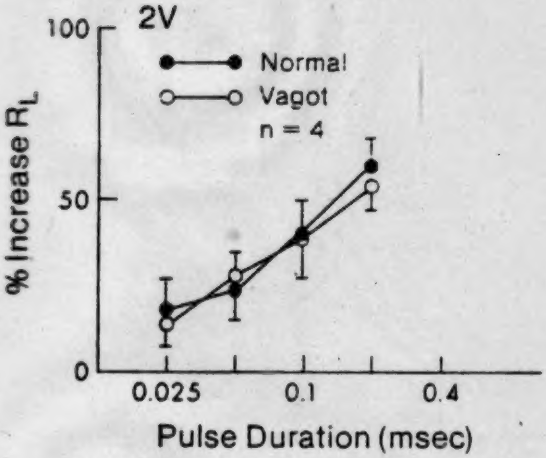

FIGURE 45. Effects of bilateral, mid-cervical vagotomy on increases in $R_L$ produced by nerve stimulation.

Vagotomy produced no significant effects on the responses to nerve stimulation. Points show mean responses and vertical lines indicate one S.E.M.

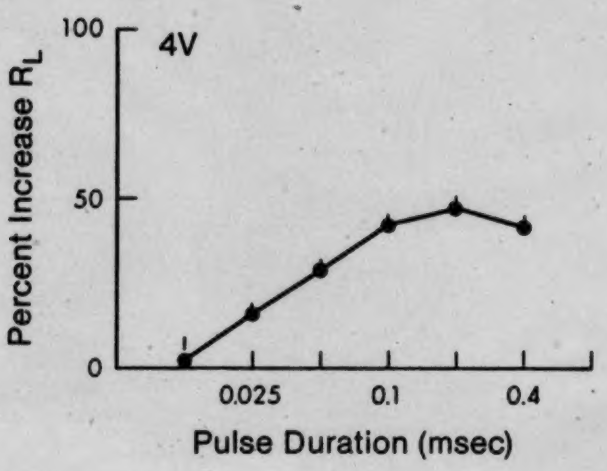

Figure 46. Mean responses to nerve stimulation obtained at intervals over periods of two to three hours.

Responses to nerve stimulation were stable and reproducible for two to three hours. The points represent the mean of four responses and the vertical lines indicate one S.E.M.

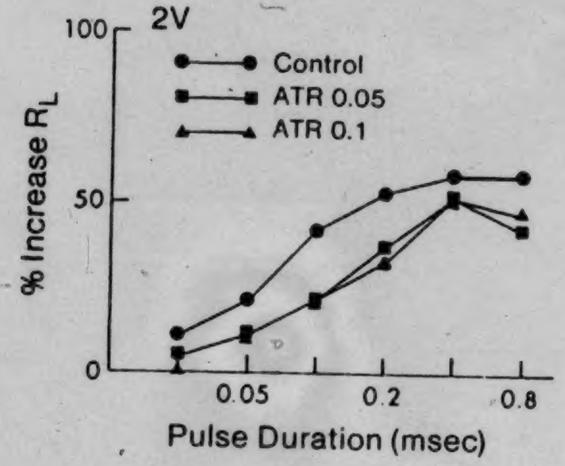

Figure 47. Effects of atropine (ATR, 0.05 & 0.1 mg/kg) on increases in $R_L$ produced by nerve stimulation.

ATR, 0.05 mg/kg, reduced the responses to nerve stimulation. Increasing the dose of ATR produced no further inhibition of the responses.

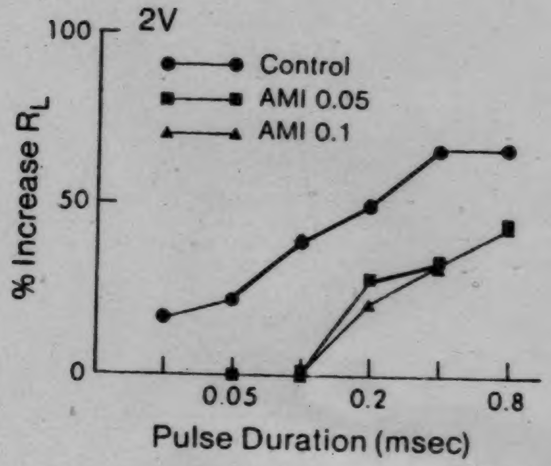

Figure 48. Effects of atropine methiodide (AMI, 0.05 & 0.1 mg/kg) on increases in $R_L$ produced by nerve stimulation.

AMI, 0.05 mg/kg, reduced the responses to nerve stimulation. Increasing the dose of AMI did not produce further inhibition of the responses.

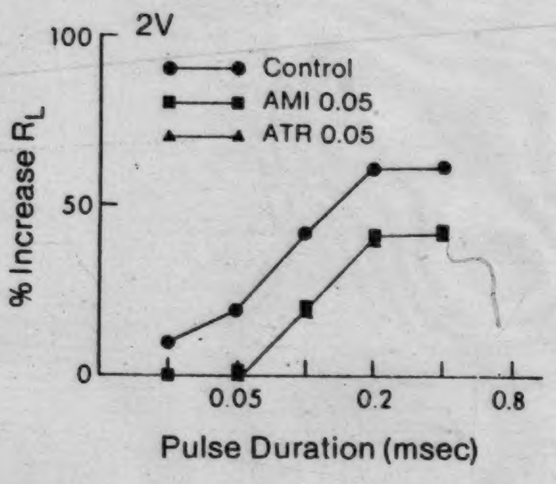

Figure 49. Effects of atropine methiodide (AMI, 0.05 mg/kg), followed by atropine (ATR, 0.05 mg/kg), on increases in $R_L$ produced by nerve stimulation.

AMI, 0.05 mg/kg, reduced the responses to nerve stimulation. Administration of ATR, 0.05 mg/kg, after AMI had been given, produced no further inhibition of the responses.

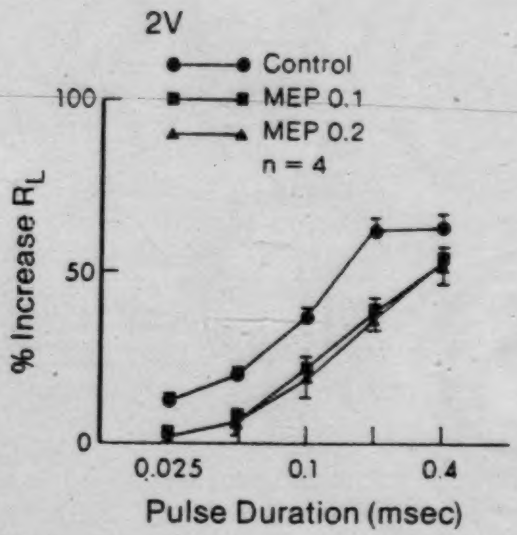

Figure 50. Effects of mepyramine (MEP, 0.1 & 0.2 mg/kg) on increases in $R_L$ produced by nerve stimulation.

MEP, 0.1 mg/kg, reduced the response to nerve stimulation. Increasing the dose of MEP produced no further inhibition of the responses. The points show mean responses and lines indicate one S.E.M.

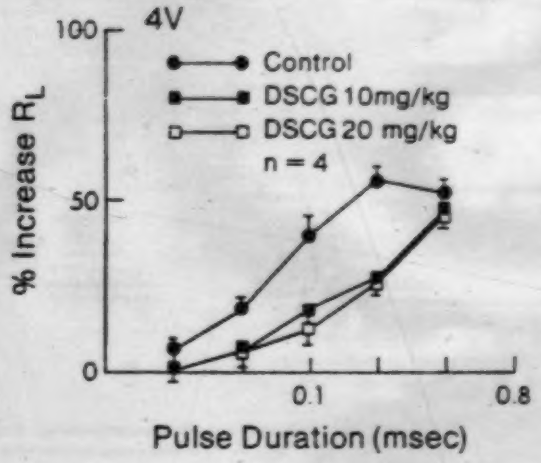

Figure 51. Effects of disodium cromoglycate (DSCG) on increases in $R_L$ produced by nerve stimulation.

DSCG, 10 mg/kg, reduced the responses to nerve stimulation. Increasing the dose of DSCG produced no further inhibition of the responses. Points show mean responses and vertical lines indicate one S.E.M.

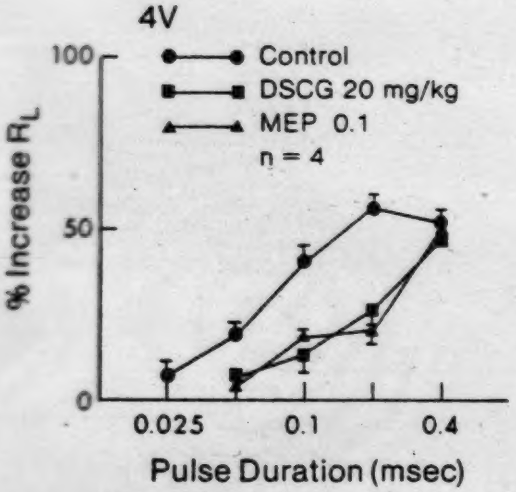

Figure 52. Effect of disodium cromoglycate (DSCG), followed by mepyramine (MEP, 0.1 mg/kg), on increases in $R_L$ produced by nerve stimulation.

After DSCG had been administered, MEP, 0.1 mg/kg, no longer reduced the responses to nerve stimulation. Points show mean responses and vertical lines indicate one S.E.M.

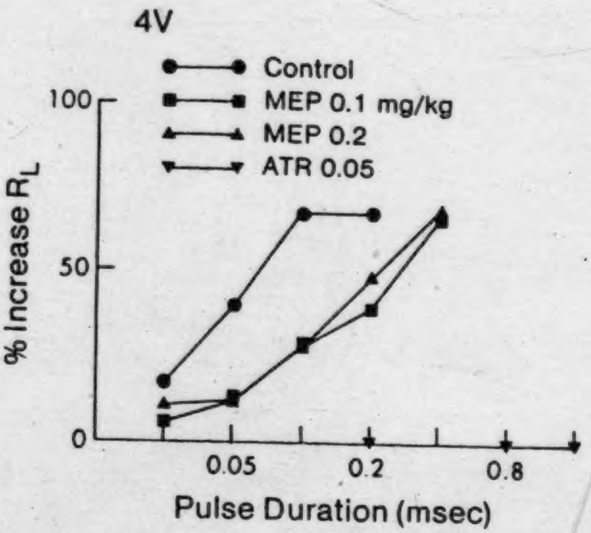

Figure 53. Effects of mepyramine (MEP, 0.1 & 0.2 mg/kg), followed by atropine (ATR, 0.05 mg/kg), on increases in $R_L$ produced by nerve stimulation.

MEP, 0.1 mg/kg, reduced the responses to nerve stimulation. Increasing the dose of MEP produced no further inhibition, but the combination of MEP and ATR, 0.05 mg/kg, eliminated the responses.

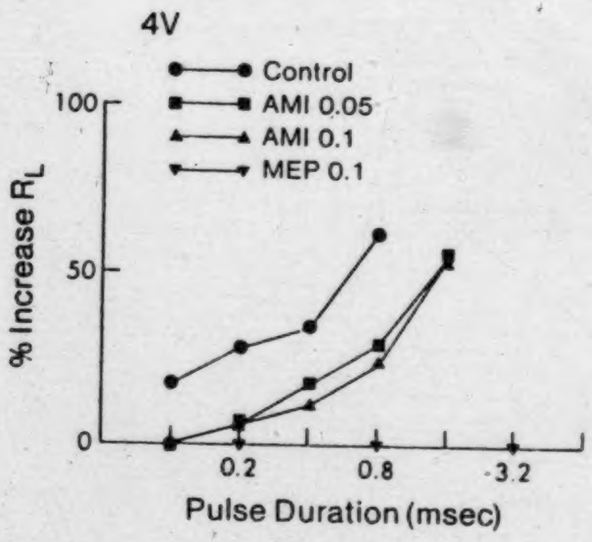

Figure 54. Effects of atropine methiodide (AMI, 0.05 & 0.1 mg/kg), followed by mepyramine (MEP, 0.1 mg/kg), on increases in $R_L$ produced by nerve stimulation.

AMI, 0.05 mg/kg, reduced the responses to nerve stimulation. Increasing the dose of AMI produced no further inhibition, but the combination of AMI and MEP, 0.1 mg/kg, eliminated the responses.

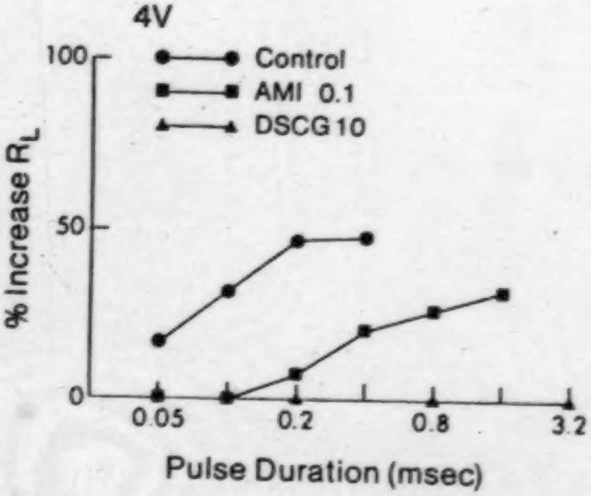

Figure 55. Effects of atropine methiodide (AMI, 0.1 mg/kg), followed by disodium cromoglycate (DSCG, 10 mg/kg), on increases in $R_L$ produced by nerve stimulation.

AMI, 0.1 mg/kg, reduced the responses to nerve stimulation, whereas the combination of AMI and DSCG, 10 mg/kg, eliminated the responses.

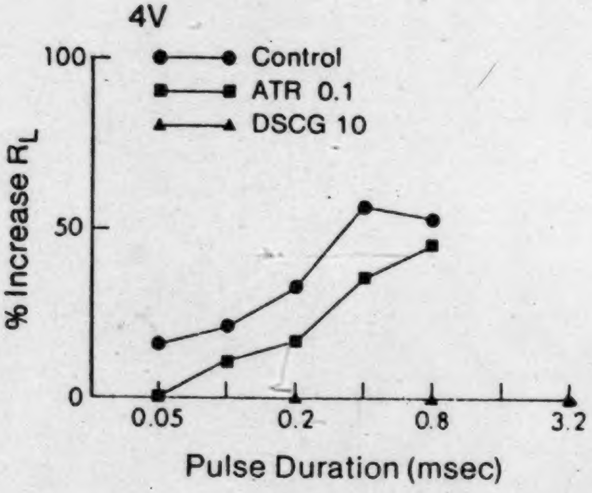

Figure 56. Effects of atropine (ATR, 0.1 mg/kg), followed by disodium cromoglycate (DSCG, 10 mg/kg), on increases in $R_L$ produced by nerve stimulation.

ATR, 0.1 mg/kg, reduced responses to nerve stimulation, whereas the combination of ATR and DSCG, 10 mg/kg, eliminated the responses.

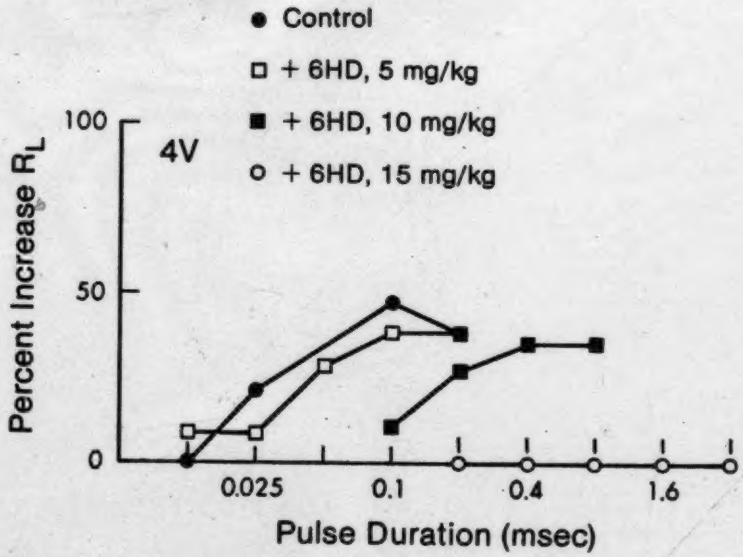

Figure 57. Effects of 6-hydroxydopamine (6HD) on increases in $R_L$ produced by nerve stimulation.

Increasing doses of 6HD progressively inhibited, and then abolished, the responses to nerve stimulation.

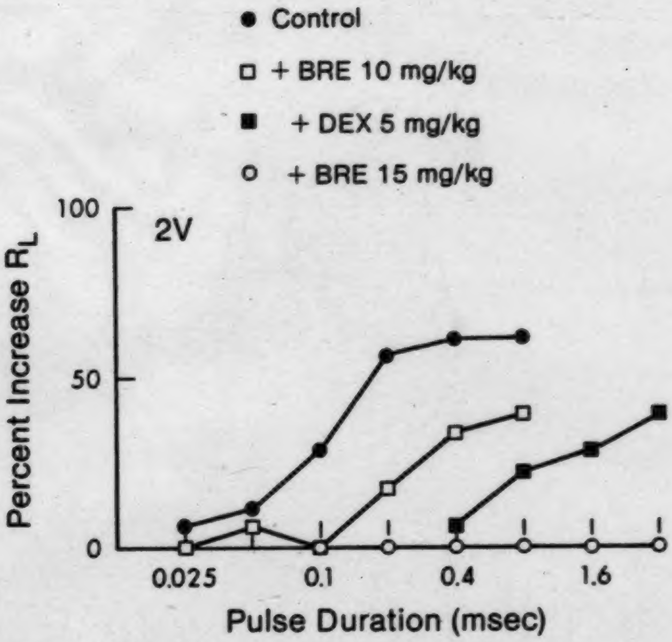

Figure 58. Effects of bretylium (BRE), and BRE followed by dexamphetamine (DEX), on increases in $R_L$ produced by nerve stimulation.

Increasing doses of BRE inhibited, and then abolished, responses to nerve stimulation. Partial recovery of the responses was observed after treatment with DEX, 5 mg/kg.

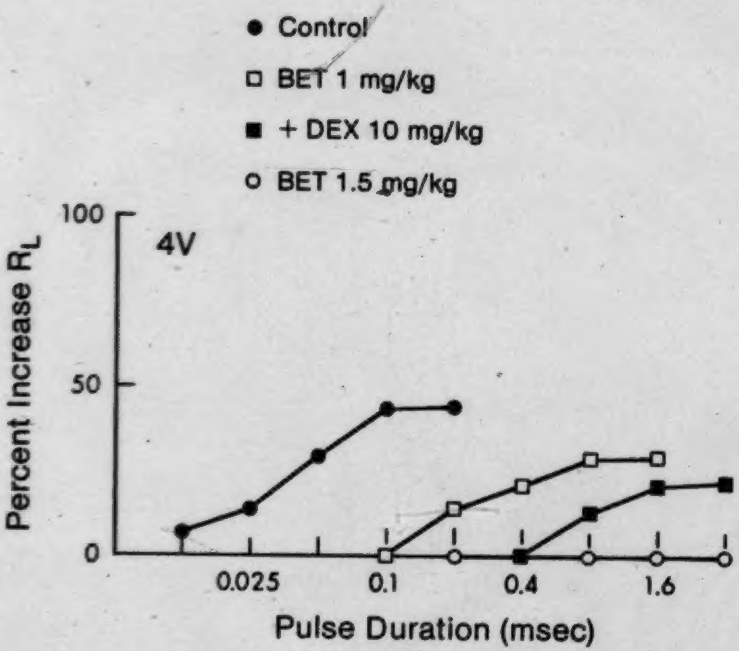

Figure 59. Effects of bethanidine (BET), and BET followed by dexamphetamine (DEX), on increases in $R_L$ produced by nerve stimulation.

Increasing doses of BET inhibited, and then abolished, responses to nerve stimulation. Partial recovery of the responses was observed after treatment with DEX 10 mg/kg.

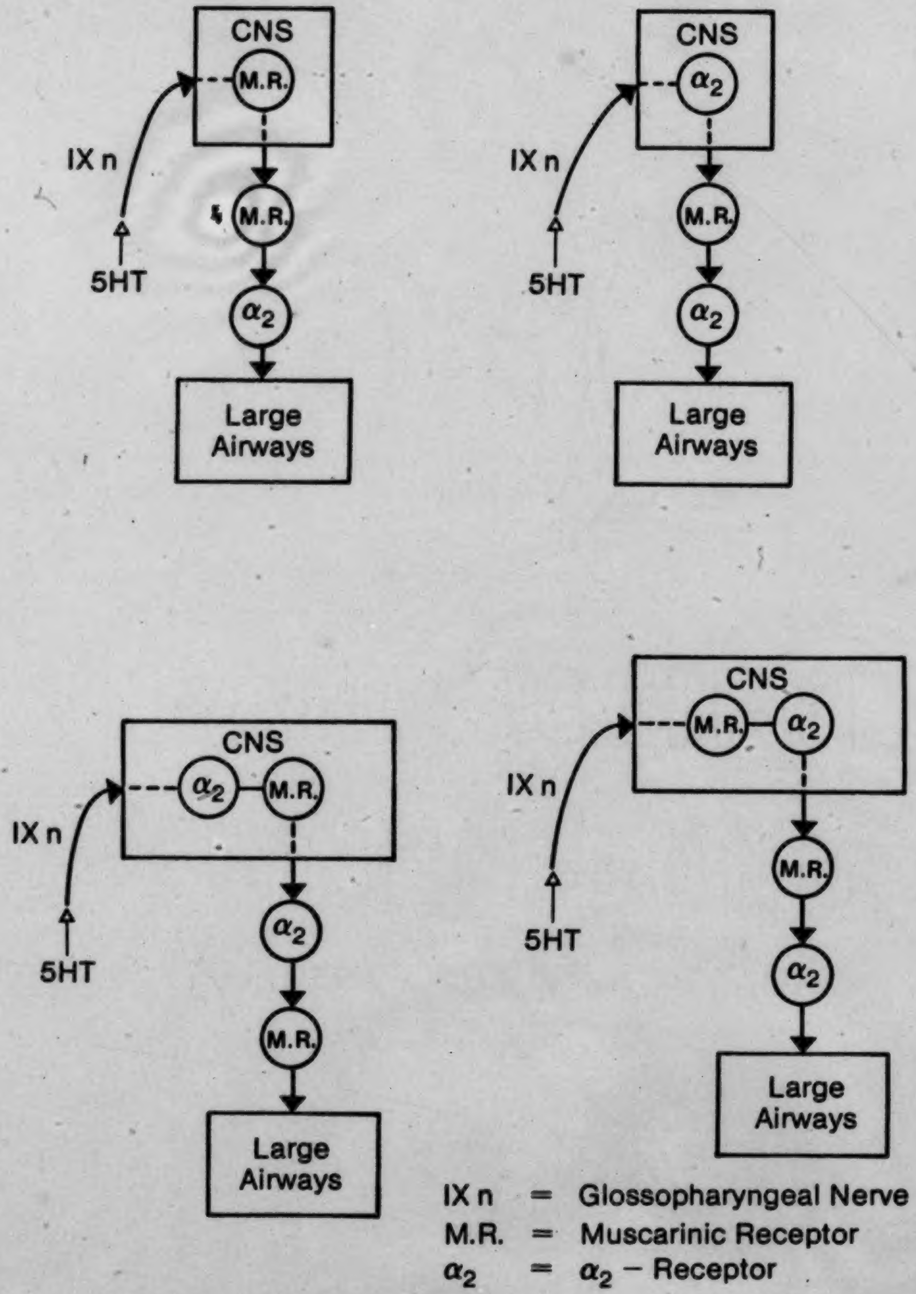
CNS
M.R.
α2
IX n
5HT
M.R.
α2
Large Airways
CNS
α2
IX n
5HT
M.R.
α2
Large Airways
CNS
α2
M.R.
IX n
5HT
α2
M.R.
Large Airways
CNS
M.R.
α2
IX n
5HT
M.R.
α2
Large Airways
IX n = Glossopharyngeal Nerve
M.R. = Muscarinic Receptor
α2 = α2 – Receptor

Figure 60. Possible reflex arcs associated with reflex actions of 5HT.

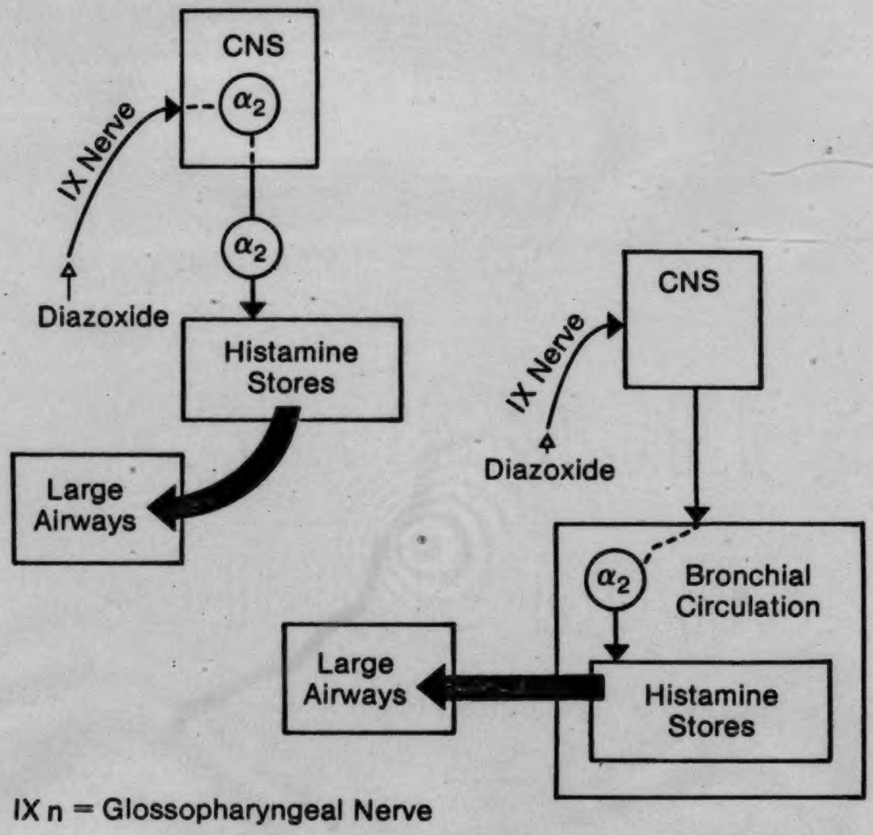
CNS
$\alpha_2$
IX Nerve
$\alpha_2$
Diazoxide
Histamine Stores
Large Airways
CNS
IX Nerve
Diazoxide
$\alpha_2$
Bronchial Circulation
Large Airways
Histamine Stores
IX n = Glossopharyngeal Nerve

Figure 61. Possible reflex arcs associated with reflex actions of diazoxide.

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## Appendix 1. Drugs and Suppliers

Atropine sulfate, BDH, Toronto, Canada

Atropine methiodide, prepared in our laboratory, pure by m.p., I.R. and N.M.R.

Azapetine phosphate, Roche, Montreal, Canada

Bethanidine sulphate, Burroughs Wellcome, La Salle, Canada

Bretylium tosylate, Burroughs Wellcome, La Salle, Canada

Clonidine hydrochloride, a gift from Boehringer Ingelheim, Burlington, Canada

Dexamphetamine sulphate, Sigma, St. Louis, U.S.A.

Diazoxide injection, a gift from Schering, Pointe Claire, Canada

Disodium cromoglycate, a gift from Fisons, Don Mills, Canada

Heparin sodium injection, BDH, Toronto, Canada

Hexamethonium bromide, K & K Laboratories, Plainview, U.S.A.

Histamine phosphate, Fisher,, New Jersey, U.S.A.

5-Hydroxytryptamine creatinine sulfate complex (serotonin), Sigma, St. Louis, U.S.A.

6-Hydroxydopamine hydrochloride, Sigma, St. Louis, U.S.A.

Mepyramine maleate, Poulenc, Montreal, Canada

Methysergide bimaleate, Sandoz, Basle, Switzerland

Pancuronium bromide injection, Organon, Toronto, Canada

Phenylephrine hydrochloride, Sigma, St. Louis, U.S.A.

Propranolol hydrochloride injection, Ayerst, Montreal, Canada

Reserpine injection, Ciba-Geigy, Dorval, Canada

Trimethaphan camphorsulfonate injection, Roche, Montreal, Canada

Tyramine hydrochloride, Sigma, St. Louis, U.S.A.

## APPENDIX 2. Sample calculations and traces used to determine $R_L$

Examples of flow rate signals and pressure signals used to determine $R_L$ are shown in Figure 2-1. Both signals were obtained from the y-axis of an EIA 1140 Variplotter slaved to the y- (flow rate) and x- (tracheal pressure) output of a Tektronix oscilloscope set up as described in Chapter 2. Figure 2-2 shows sample loops obtained when the flow rate was plotted against pressure. Loop A is a control loop produced when the flow rate was plotted against the total pressure signal over a respiratory cycle. Loop B shows the same loop after the compliance portion of the pressure signal had been subtracted; a linear plot resulted from the subtraction. Loop C shows the control loop after more than the compliance component of the pressure signal had been subtracted; linearity was lost and the loop became inverted. Loops D and E show loops obtained (with the compliance component of the pressure signal subtracted) after the administration of 4 and 8 $\mu$g/kg of 5HT, respectively.

The value of $R_L$ was computed as 1/slope of the linear 'flow rate-pressure' curve which is equibalent to $1/\tan\theta$ , where  is the angle between the linear plot and the x-axis (see Figure 2-2, Loops B and D). In order to have the value of $R_L$ in the correct units, the value of tan  was multiplied by a calibration factor calculated as follows:

a) A 1 cm change on the y-axis was equivalent to a flow rate change of 30.6 ml/s,

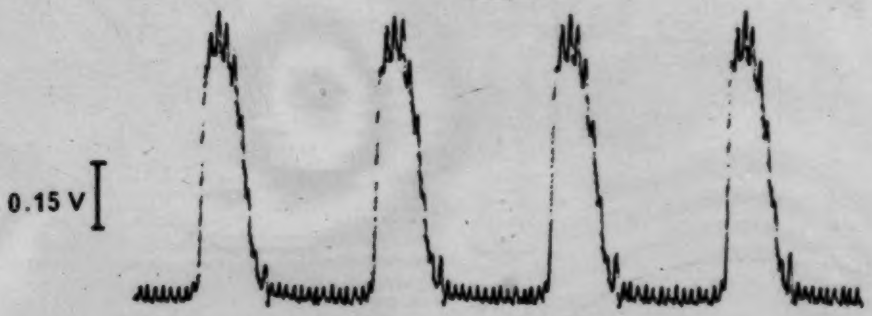
b) A 1 cm change on the x-axis was equivalent to a pressure change of 21.5 cm $H_2O$,

c) Therefore a unit change of y and x represented a change of 30.6/21.5 ml/s/cm $H_2O$,

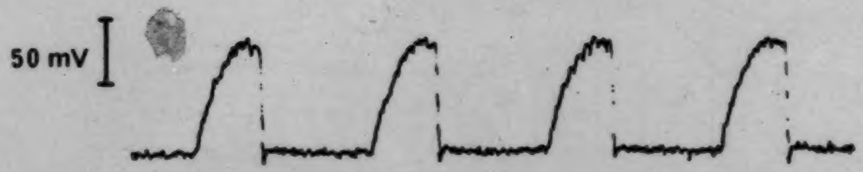
d) For correct units to be obtained, $R_L$ was therefore calculated as 1/0.55 tan $\theta$ cm $H_2O$/ml/s.

In Loop B, the angle $\theta$ was 85° and the value of $R_L$ was therefore equal to 1/0.55 tan 85° or 0.16 cm $H_2O$/ml/s. Similarly, after 4 μg/kg of 5HT had been given (Loop E) the value of $R_L$ was equal to 1/0.55 tan 80° or 0.32 cm $H_2O$/ml/s.

The change in $R_L$ was therefore calculated as (0.32 - 0.16)/0.16 x 100 or 100%.

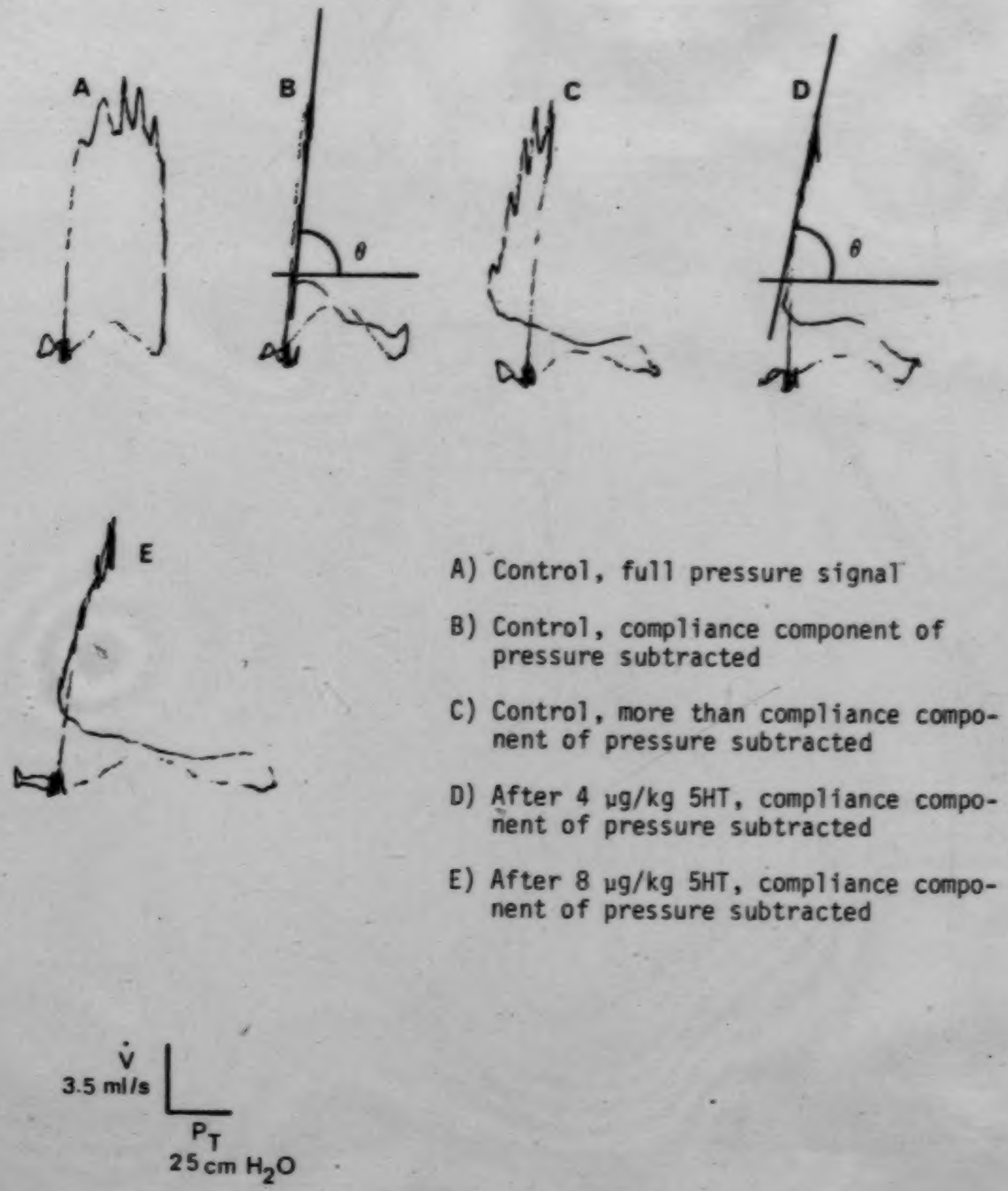


A. Trace of tracheal pressure measured during ventilation at respiratory volume of 7 ml



B. Trace of flow rate measured during ventilation at respiratory volume of 7 ml

FIGURE 2-1. Flow rate and pressure traces



A) Control, full pressure signal

B) Control, compliance component of pressure subtracted

C) Control, more than compliance component of pressure subtracted

D) After 4 μg/kg 5HT, compliance component of pressure subtracted

E) After 8 μg/kg 5HT, compliance component of pressure subtracted

FIGURE 2-2. Sample loops obtained by plotting flow rate signals and pressure signals during respiratory cycle.

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|---|---|---|---|
| B.Sc. with Distinction | 1974 | Pharmacy | University of Alberta |
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AWARDS:

Pfizer Research Scholarship, 1974

Medical Research Council of Canada Graduate Studentship, 1974-1978

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RESEARCH AND PROFESSIONAL EXPERIENCE:

Sept. 1980 - present: Sessional Lecturer, Faculty of Pharmacy & Pharmaceutical Sciences

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1978 - 1980: Graduate Teaching Assistant (GTA)

March 1980 - Jan. 1981: House Committee, Graduate Student Association.

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March 1978-Sept. 1980: Graduate Student Association Representative for Faculty of Pharmacy

1974 -1978: GTA while receiving training in general and respiratory pharmacology

1971-1974: Received training for pharmacy degree

1974 - present: Alberta Pharmaceutical Association member

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PAPERS AND PUBLICATIONS:

Demajo, W., Biggs, D.F. & Peterson, M. (1977). A comparison of the bronchodilator effects of diazoxide, aminophylline and isoproterenol, presented at Annual Meeting of the Canadian Tuberculosis & Respiratory Disease Association, Clinical Section, Moncton.

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